Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

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I. 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.

For individuals who have BE with high-grade dysplasia (HGD) who receive endoscopic RFA, the evidence includes a randomized controlled trial (RCT) comparing radical endoscopic resection with focal endoscopic resection followed by RFA, an RCT comparing RFA with surveillance alone, and a number of observational studies, some of which compared RFA with other endoscopic treatment modalities. Relevant outcomes are overall survival, 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 a meaningful improvement in the net health outcome.

For individuals who have BE with low-grade dysplasia (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 overall survival, 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; making the 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 a meaningful improvement in the net health outcome.

Based on the results of available evidence from RCTs and other evidence sources relevant to RFA for BE with LGD, along with specialty society guidelines, clinical input was obtained. Input generally supported the use of RFA for BE with LGD. Input indicated that it is possible to define a population with a higher risk of progression by having the initial diagnosis of LGD reconfirmed by an expert in gastrointestinal pathology.

For individuals who have BE without dysplasia who receive endoscopic RFA, the evidence includes single-arm studies reporting outcomes after RFA. Relevant outcomes are overall survival, 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 the effects of the technology on health outcomes.

For individuals who have BE with or without dysplasia who receive endoscopic cryoablation, the evidence includes noncomparative studies reporting outcomes after cryoablation. Relevant outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. These studies 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 the effects of the technology on health outcomes.

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 (GERD). BE occurs in the distal esophagus, may be of any length, 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 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 study 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). 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%. 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.

Management

The management of BE includes treatment of gastroesophageal reflux disease (GERD) 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 study provided long-term results for EMR in 100 consecutive patients with early Barrett-associated adenocarcinoma (limited to the mucosa). 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, the authors state 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%.

Ablation Techniques

Available mucosal ablation techniques that include several thermal (multipolar electrocoagulation [MPEC], argon plasma coagulation [APC], heater probe, Nd:YAG laser, KTP-YAG laser, diode laser, argon laser, and cryoablation) or nonthermal (5-ALA and Photofrin photodynamic therapy [PDT]) techniques. In a randomized phase 3 trial, PDT has been shown to significantly decrease the risk of adenocarcinoma in BE.

The CryoSpray Ablation™ system (formerly the SprayGenix™ Cryo Ablation system; CSA Medical, Lutherville, MD) uses a low-pressure spray for spraying liquid nitrogen through an upper endoscope. Cryotherapy allows for treatment of uneven surfaces; however, a disadvantage is the uneven application inherent in spraying the cryogen.

The HALO system from Barrx™ Medical (Sunnyvale, CA; acquired by Covidien in 2012, and now known as the Barrx line of products) uses radiofrequency (RF) energy and consists of 2 components, an energy generator and an ablation catheter. The generator provides rapid (ie, <1 second) delivery of a predetermined amount of RF 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. The HALO360 uses a balloon catheter that is sized to fit the individual's esophagus and is inflated to allow for circumferential ablation.

Ablation with RF affects only the most superficial layer of the esophagus (ie, the mucosa), leaving the underlying tissues unharmed. Measures of efficacy for the procedure are eradication of intestinal metaplasia, without leaving behind microscopic (or "buried") foci, and postablation regrowth of the normal squamous epithelium. Reports of the efficacy of the HALO system in ablating BE have been as high as 70% (comparable with alternative methods of ablation [eg, APC, MPEC]), and even higher in some reports. The incidence of leaving behind buried 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%. Another potential advantage to the HALO system is that because it is an automated process, it eliminates operator-dependent error that 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.

REGULATORY STATUS

In 2005, the HALO360 (now Barrx™ 360 RFA Balloon Catheter; Barrx Medical, Sunnyvale, CA; acquired by Covidien in 2012) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and, in 2006, the HALO90 (now Barrx™ 90 RFA Focal Catheter) received clearance. FDA-labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract, and include the treatment of BE.7 FDA product code: GEI.

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

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

II. **Criteria/Guidelines**
   A. Radiofrequency ablation is covered (subject to Limitations and Administrative Guidelines) for the treatment of Barrett esophagus with high-grade dysplasia see Policy Guidelines) prior to the procedure**.**
   B. Radiofrequency ablation is covered (subject to Limitations and Administrative Guidelines) for treatment of Barrett esophagus with low-grade dysplasia, when the initial diagnosis of low-grade dysplasia is confirmed by 2 physicians (see Policy Guidelines) prior to the procedure.

III. **Policy Guidelines**

Radiofrequency ablation for BE with high-grade dysplasia (HGD) may be used in combination with endoscopic mucosal resection of nodular/visible lesions. The diagnosis of HGD should be confirmed by two pathologists before RFA.
There is considerable interobserver variability in the diagnosis of low-grade dysplasia (LGD), and the potential exists for overdiagnosis of LGD by nonexpert pathologists. This is due primarily to the difficulty in distinguishing inflammatory changes from LGD. There is literature evidence 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). As a result, it is ideal that two experts in GI 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 GI pathologist will also result in a large number of LGD diagnoses being downgraded,

although probably not as many downgrades as achieved by using two expert pathologists (Kerkhof et al, 2007).

IV. Limitations

A. Radiofrequency ablation is not covered 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 as it is not known to improve healthoutcomes.

B. Cryoablation is not covered for the treatment of Barrett esophagus, with or without dysplasia as it is not known to improve healthoutcomes.

V. Administrative Guidelines

A. Precertification is not required. The following documentation must be kept in the patient's medical record and made available upon request:
1. Current history and physical documenting the patient's condition
2. Pathology reports confirming the diagnosis of either high-grade dysplasia or low-grade dysplasia by at least two pathologists.

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

CPT Code	Description
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)

VI. Scientific Background

This evidence review was created in December 2008 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through September 14, 2017.

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

RADIOFREQUENCY ABLATION FOR BARRETT ESOPHAGUS

Radiofrequency Ablation vs Surgical Resection for Barrett Esophagus With Dysplasia

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

Systematic Reviews

In 2014, Chadwick et al reported on a systematic review that compared RFA with complete endoscopic mucosal resection (EMR) for treatment of Barrett esophagus (BE).14 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 the RCT by van Vilsteren et al (2011)15; the other RCT was by Shaheen et al (2009, 2011; see below). The studies were heterogeneous in design. A total of 1087 (532 EMR, 555 RFA) patients with high-grade dysplasia (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 two. 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 ER patients.

In 2013, Orman et al reported on a systematic review and meta-analysis of 24 studies with a total of 4342 patients treated with RFA for BE dysplasia and intestinal metaplasia.18 Included in this review were the studies by van Vilsteren et al and Shaheen et al.15-17 The studies reviewed were heterogeneous in design and contained a mix of nondysplastic and low-grade dysplasia (LGD) and HGD. The use of EMR to treat patients varied in the studies, ranging from 0% to 96%. Patients were followed for a median of 20.5 months (range, 12-31 months). For patients treated with RFA, complete eradication of dysplasia occurred in 91% (95% confidence interval [CI], 87% to 95%), and complete eradication of intestinal metaplasia occurred in 78% (95% CI, 70% to 86%). Intestinal metaplasia recurred in 13% (95% CI, 9% to 18%) after eradication. In patients with complete eradication of intestinal metaplasia, 0.2% and 0.7% progressed to cancer during treatment and after treatment, respectively. The most frequent adverse event observed was esophageal stricture, which occurred in 5% of patients (95% CI, 3% to 7%).

Semlitsch et al (2010) reported a systematic review of the evidence for RFA of BE based on a total of 9 observational studies (total N=429 patients).19 Selection criteria required that studies include patients with BE and metaplasia or dysplasia for which RFA was the intervention (with or without EMR) and have a minimum follow-up period of 12 months. In seven of the studies, patients were treated with circumferential ablation followed by focal ablation, whereas two used only the circumferential method. The maximum number of ablations performed was reported in 7 studies (range, 2-5 ablations). Complete eradication of BE with dysplasia and BE with metaplasia was achieved in 71% to 100% and 46% to 100% of patients, respectively. Six cases of esophageal

stenosis and a case of buried intestinal metaplasia were reported among all patients.

Randomized Controlled Trials
Van Vilsteren et al (2011) reported on the results of a multicenter, randomized trial 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 containing HGD or early cancer. Patients in the SRER group underwent 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 (CR-neoplasia); and complete histologic response for intestinal metaplasia (CR-IM). CR-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<0.001), resulting in more therapeutic sessions in SRER (6 vs 3; p<0.001), due to dilations. After a median follow-up of 24 months, 1 SRER patient had recurrence of early cancer, requiring endoscopic resection. This trial confirmed that both techniques achieved comparably high rates of CR-IM and CR-neoplasia but found that SRER was associated with more complications and therapeutic sessions.

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

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

RFA vs Surveillance Alone for BE

RFA for Dysplastic BE
One randomized multicenter, sham-controlled trial has compared RFA with surveillance alone in BE

with dysplasia. This trial, by Shaheen et al, included patients with both HGD and LGD. A total of 127 patients with dysplastic BE were randomized in a 2:1 ratio to RFA or a sham procedure. The groups were assigned by grade of dysplasia (low grade [n=64] or high grade [n=63]) and length of the tissue lining with BE (<4 cm or 4-8 cm). Patients in the RFA group could receive up to 4 ablation sessions, performed at baseline and at 2, 4, and 9 months. Primary outcomes were the proportion of patients who had complete eradication of dysplasia at 12 months and the proportion of all patients who had complete eradication of intestinal metaplasia at 12 months. The proportion of patients who had progression of dysplasia was a secondary outcome; this included progression of LGD to HGD or cancer, and the progression of HGD to cancer. This trial was included in a 2010 TEC Assessment and was rated fair on formal quality assessment using U.S. Preventive Services Task Force criteria. The only obstacles to a good rating were missing details about random sequence generation and concealment of allocation.

Overall, complete eradication of intestinal metaplasia was 77.4% in the ablation group compared with 2.3% of the control group (p<0.001). Patients who did not receive RFA were more likely to have disease progression (16.3%) than those who received RFA (3.6%; p=0.03). Three serious adverse events occurred in the RFA group, including an episode of upper gastrointestinal hemorrhage, which was treated endoscopically, an overnight hospitalization for new-onset chest pain 8 days after RFA, and 1 night of hospitalization for an episode of chest discomfort and nausea immediately after RFA. No adverse events were observed in the control group. No esophageal perforations or procedure-related deaths occurred. Among patients in the RFA group, esophageal stricture developed in 5 (6%) patients, all of whom successfully underwent dilated endoscopy.

In 2011, 2- and 3-year results of this trial were reported. Subjects were followed for a mean period of 3.05 years, with 106 (83%) of 127 patients included in the analysis. Outcomes were eradication of dysplasia or intestinal metaplasia after 2 and 3 years, durability of response, disease progression, and adverse events. After 2 years, 101 (95%) of 106 patients had complete eradication of all dysplasia and 99 (93%) of 106 had eradication of intestinal metaplasia. Serious adverse events occurred in 4 (3.4%) of 119 subjects. No perforations or procedure-related deaths occurred. The rate of esophageal stricture was 7.6%. The rate of esophageal adenocarcinoma was 1 per 181 patient-years (0.55%/patient-years); there was no cancer-related morbidity or mortality. The annual rate of any neoplastic progression was 1 per 73 patient-years (1.37%/patient-years). The authors concluded that, for patients with dysplastic BE, RFA was durable and associated with a low rate of disease progression for up to 3 years.

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

RFA for HGD
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 13% or less. Therefore, intervention with esophagectomy or RFA may be strongly indicated.

The 2009 RCT conducted by Shaheen et al reported that RFA was successful in eradicating HGD, with complete eradication at 12 months achieved in 81% of the ablation group vs 19% in the control group (p<0.001).16 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 vs 2.4% in the RFA group (p=0.04). This represented a nearly 90% relative risk (RR) reduction for progression to cancer (RR=0.1; 95% CI, 0.01 to 1.0, p=0.04), and a number needed to treat of 6.0 to prevent 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. 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.

RFA may be used alongside focal endoscopic resection. In the ITT analysis of a prospective interventional study (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. At a median follow-up of 27 months, neoplasia or intestinal metaplasia had recurred in 4% and 8% of subjects, respectively.

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

Section Summary: RFA for HGD
For patients 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, progression from HGD to cancer is reduced by approximately 90%, with rates of esophageal strictures of 6%.

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

of cancer or HGD was 10.77 per 1000 patient-years (95% CI, 2.22 to 31.48 per 1000 patient-years). For RFA-treated patients, pooled rates of complete eradication of intestinal metaplasia and complete eradication of dysplasia were 87.2% (95% CI, 76.2% to 93.5%) and 90.6% (95% CI, 81.0% to 95.6%), respectively.

The 2010 TEC Assessment evaluated the use of RFA plus surveillance vs surveillance alone in the treatment of nondysplastic and LGD BE and included the Shaheen RCT as well as 4 single-arm studies; it determined that the evidence was insufficient to permit conclusions on the use of RFA for patients with nondysplastic or LGD BE.

Since the TEC Assessment and the 2014 Almond systematic review, an RCT comparing RFA with surveillance in patients with LGD was published by Phoa et al (2014). 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 ITT 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 complete eradication of dysplasia, the absence of intestinal metaplasia, and adverse events.

The trial was terminated early after interim analysis determined the superiority of RFA. 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<0.03), and the occurrence of HGD was also significantly lower for the RFA group (1.5%) than for the surveillance group (26.5%; p<0.001). For patients treated with RFA, complete eradication of dysplasia during follow-up was 98.4% and the absence of metaplasia was 90.0%. There were 3 serious adverse events in 2 patients who received RFA (1 abdominal pain requiring hospitalization, 1 bleeding episode, 1 episode of fever/chills following dilation for stricture), and 12 other adverse events (8 strictures requiring dilation, 3 mucosal lacerations, 1 retrosternal pain).

In the Shaheen RCT, there were 64 patients with LGD for which subgroup analysis was reported. At 12-month follow-up, dysplasia was completely eradicated in 90.5% of those in the RFA group compared with 22.7% of those in the control group (p<0.001). No patients in the LGD group progressed to cancer over the initial 12 months. Progression to HGD was noted in 2 (5%) of 42 patients in the RFA group compared with 3 (14%) of 22 in the control group. The difference in rates of progression to HGD was not statistically significant (RR=0.3; 95% CI, 0.1 to 1.9; p=0.33). After 2 years, 52 subjects were available who had initial LGD treated with RFA. Progression from LGD to HGD or cancer occurred in 1 patient, for an estimated rate of 2.0% per patient-year. In patients with initial LGD, all dysplasia was eradicated in 51 (98%) of 52, and all intestinal metaplasia was eradicated in 51 (98%) of 52.

Selection of Patients With LGD
There are challenges in diagnostically differentiating between nondysplastic BE and BE with LGD;

they are important when considering treatment for LGD. Both sampling bias and interobserver variability have been shown to be problematic. Therefore, analysis of progression to carcinoma in BE with intestinal metaplasia vs 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.

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 vs inflammatory changes, and the resultant variability in pathology diagnosis may contribute to the variable rates of progression of LGD reported in the literature.21 Kerkhof et al (2007) reported that, in patients with an initial pathologic diagnosis of LGD, review by an expert pathologist will result in the initial diagnosis being downgraded to nondysplasia in up to 50% of cases.29 Curvers et al (2010) tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD.30 All pathology slides were read by 2 expert GI pathologists with extensive experience in BE; any 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 the 2014 Phoa RCT, which required confirmation of LGD by a central expert panel following initial diagnosis by a local pathologist.25 Of 511 patients with an initial diagnosis of LGD, 264 (52%) were excluded because the central expert panel reassigned classification of LGD, most often from LGD to indefinite or nondysplasia. These findings were further confirmed in a 2015 retrospective cohort study of 293 BE cases with LGD diagnosed over an 11-year period and submitted for expert panel review.31 In this sample, 73% of subjects were downstaged.

Section Summary: RFA for LGD

The risk of progression from LGD to cancer is not well-defined, with highly variable rates reported in the published literature. Evidence from randomized and nonrandomized studies has established that RFA can achieve complete eradication of dysplasia in patients with LGD that is durable for at least 2 years. One RCT of 136 subjects reported a lower rate of progression to HGD or adenocarcinoma for patients who had confirmed LGD treated with RFA. This trial supports the strategy of selecting a population that has a higher risk of progression by subjecting the initial pathologic diagnosis of LGD to review by an expert in GI pathology. Expert review has 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.

RFA for BE Without Dysplasia

No RCTs were identified that evaluate RFA treatment of BE without dysplasia. The evidence on this issue consists of single-arm trials that have reported outcomes of RFA. This evidence can provide

useful data on the success in eradicating dysplasia; however there is no high-quality evidence on the comparative efficacy of RFA vs 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%.

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. The original study included 70 patients who underwent circumferential RFA and CR-IM, defined as complete eradication of nondysplastic BE. CR-IM was seen in 70% of patients at 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. 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. 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 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 lent support to the safety, efficacy, cost utility, and reduction in neoplastic progression in treating nondysplastic BE with RFA.

Section Summary: RFA for Nondysplastic BE

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

RFA vs Photodynamic Therapy for BE

In 2013, Ertan et al reported on a series of 86 consecutive patients treated with either photodynamic therapy (PDT) or RFA by a single investigator. RFA was administered to 47 patients with LGD and 6 patients with HGD. PDT was administered to 33 patients with HGD. Average time from ablative therapy to follow-up biopsy was 33 months (range, 24-48 months) for RFA and 44 months (range, 24-60 months) for PDT. RFA resulted in significantly more complete eradication of dysplasia (88.7%) than PDT (54.5%; p=0.001). However, interpretation of this study is limited by its nonrandomized nature and differences in the type of dysplasia between groups.

In a retrospective observational study of BE patients with HGD or adenocarcinoma, David et al (2015) compared several endovascular therapies, including RFA, EMR plus RFA, and PDT. Of the 342 patients included, 98 underwent EMR plus RFA, 119 had RFA alone, and 125 received PDT. Patients treated with PDT were typically older, had more advanced stages of BE, and had more comorbidities. In multivariable analysis, complete remission of intestinal metaplasia was more likely in those patients who received PDT than in those treated with EMR plus RFA (RR=2.69; p<0.001) or RFA alone (RR=4.47; p<0.001). However, the multivariable analysis did not adjust for a

history of esophageal cancer, esophagectomy, or warfarin use. Among 121 patients who had at least 1 follow-up visit after complete remission of intestinal metaplasia was established, the disease recurrence rate was 32.2%, which did not differ across treatment groups.

Section Summary: RFA vs Photodynamic Therapy for BE
There is limited evidence to compare RFA with PDT for treatment of BE. There are no controlled trials, and the nonrandomized studies have provided mixed findings about the comparative efficacy of RFA compared with PDT.

CRYOABLATION OF BE
Published efficacy data for cryoablation in BE are limited. Johnston et al (2005) conducted a prospective, single-center pilot study in 11 men with BE and degrees of dysplasia ranging from none to multifocal HGD. The mean length of BE was 4.6 cm (range, 1-8 cm). At 6-month follow-up, complete histologic eradication of BE was achieved in 7 (78%) of 9 patients, completing the protocol.

A 2009 open-label, single-center, prospective, nonrandomized cohort study assessed the safety of cryoablation as a treatment option for BE with HGD or intramucosal carcinoma.37 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 period of 12 months, elimination of cancer or downgrading of HGD was 68% for HGD and 80% for intramucosal carcinoma.

Greenwald et al (2010) reported on the safety, tolerability, and efficacy of low-pressure liquid nitrogen spray cryotherapy in 77 patients from multiple institutions who underwent a total of 377 procedures for BE with HGD (58.4%), intramucosal carcinoma (16.9%), invasive carcinoma (13%), BE without dysplasia (9.1%), and severe squamous dysplasia (2.6%). The main outcome measurement was the incidence of serious adverse events and adverse events from treatments. The most common were chest pain (18%), dysphagia (13%), odynophagia (12.1%), and sore throat (9.6%). Esophageal stricture occurred in 3 patients, all of whom were successfully treated with dilation, and gastric perforation in 1 patient. No adverse effects were reported by 28.6% of patients. Complete response for HGD, any dysplasia, intestinal metaplasia, and cancer were assessed in patients completing therapy during the study period and having at least 1 follow-up endoscopy with biopsy for assessment of histologic regression of the underlying lesion (n=23). For patients with HGD (n=17), complete response of the HGD, any dysplasia, and intestinal metaplasia were 94%, 88%, and 53%, respectively. For patients with intramucosal carcinoma (n=4), complete response was 100% for cancer, HGD, and any dysplasia, and 75% for intestinal metaplasia. For patients with invasive cancer (n=3), complete response was 100% for cancer, HGD, and any dysplasia, and 67% for intestinal metaplasia.

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. 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 by 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 the limitations of the study: it 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).

In 2015, Canto et al reported on a retrospective, single-center study that evaluated a carbon dioxide cryosurgery device for treatment of patients with neoplasia or HGD who were treatment-naive or who had persistent or recurrent neoplasia after initial treatment. The study's analysis included 68 patients who were offered treatment with cryoablation for either initial therapy (n=21) or after previous therapy with any ablative technique (n=47). At 1-year, complete response for dysplasia was 89% (57/64) overall, and 95% (19/20) and 86% (38/44) in treatment-naive and previously treated patients, respectively. Over a median follow-up of 4.2 years, the differences in complete response for HGD at 3 years or study end was not statistically significant between treatment-naive (100%) and previously treated (84%) patients (p=0.08).

Also in 2015, a retrospective, single-center study by Sengupta et al evaluated cryoablation among 16 patients who failed RFA. 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 adequate follow-up. Fourteen of those who did not have complete eradication and two who had 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.

Section Summary: Cryoablation of BE

There are no controlled trials evaluating 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 an RCT comparing radical endoscopic resection with focal endoscopic resection followed by RFA, an RCT comparing RFA with surveillance alone, and a number of observational studies, some of which compared RFA with other endoscopic treatment modalities. Relevant outcomes are overall survival, 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 a meaningful 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 overall survival, 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; making the 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 a meaningful improvement in the net health outcome.

For individuals who have BE without dysplasia who receive endoscopic RFA, the evidence includes single-arm studies reporting outcomes after RFA. Relevant outcomes are overall survival, 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 the effects of the technology on health outcomes.

For individuals who have BE with or without dysplasia who receive endoscopic cryoablation, the evidence includes noncomparative studies reporting outcomes after cryoablation. Relevant outcomes include overall survival, change in disease status, morbid events, and treatment-related morbidity and mortality. These studies 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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Clinical Input Received Through 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, three indicating that it should be medically necessary, and two indicating that it was a split decision. There was a general consensus among

reviewers that there are subpopulations of patients with LGD who have higher risk and should therefore be treated. Reviewers mentioned that factors useful in defining higher-risk populations in 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 a total of 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 BE with HGD. The reviewers were split for the use of RFA for LGD, with nine in favor of it being medically necessary and four considering it investigational.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Gastroenterology

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

Table 1: American College of Gastroenterology Guidelines

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

British Society of Gastroenterology

In 2014, the British Society of Gastroenterology published guidelines on the diagnosis and management of BE, which make the following recommendations related to the use of: For the management of dysplasia and early cancer(see Table 2).

Table 2: Guidelines on the Diagnosis and Management of Barrett Esophagus

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

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

American Society for Gastrointestinal Endoscopy

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

Table 3: British American Society for Gastrointestinal Endoscopy Guidelines

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

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

American Gastroenterological Association

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

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

Recommendation	Agreement	Strongly agree	Agree	Neither	Disagree	Strongly Disagree
Statements with ≥80% consensus agreement but generally low-quality evidence relevant to RFA for BE						
In patients with BE undergoing endoscopic therapy, endoscopic resection of more than two-thirds of the circumference is not generally recommended due to the risk of stricture.	83	13	70	17		

RFA is an acceptable treatment option for BE patients with flat mucosa containing HGD without any visible lesions confirmed by high-resolution, high-definition endoscopy.	87	35	52	13		
Statements with consensus agreement <80% relevant to RFA for BE						
In patients with BE, all cases of possible dysplasia (indefinite, low grade, high grade) should be reviewed by at least 2 additional pathologists with specific expertise in Barrett's pathology.	60.8			8.7	26.1	4.3

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

A 2011 American Gastroenterological Association medical position statement on the management of BE recommends endoscopic eradication therapy with RFA, photodynamic therapy or endoscopic mucosal resection rather than surveillance for treatment of patients with confirmed HGD within BE. The Association also stated that:

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

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

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

Table 5: Guidelines on Surgical Treatment of Gastroesophageal Reflux Disease

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

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

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

Primary Treatment

"The goal of endoscopic therapy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and/or ablation, is the complete removal or eradication of early-stage disease (pTis, pT1a, and selected superficial pT1b without lymphovascular invasion (LVI)) and pre-neoplastic tissue (Barrett's esophagus).

In early stage disease, Barrett's esophagus associated with flat high-grade dysplasia (HGD) should be treated by endoscopic resection (ER) as it provides more accurate histologic assessment of the lesion. Larger flat lesions (>2 cm) can be treated effectively by ER, but this is associated with greater risk of complications. Such lesions can be effectively treated by ablation alone, but there are very limited data on treating squamous cell HGD by ablation alone.

Lesions that are found to be pathologically limited to the lamina propria or muscularis mucosae (pT1a), or the superficial submucosa (pT1b), in the absence of evidence of lymph node metastases, LVI, or poor differentiation grade can be treated with full ER. Ablative therapy of residual Barrett's esophagus should be performed following ER. Complete eradication of Barrett's esophagus can also be performed with more aggressive application of EMR (wide field EMR) or ESD at the initial intervention, if necessary to completely resect an area of superficial tumor or mucosal nodularity less than or equal to 2 cm in maximal dimension."

Post-Treatment Surveillance
"Ablative therapy of residual Barrett's esophagus should be performed following ER. Complete eradication of Barrett's esophagus can also be performed with more aggressive application of EMR (wide field EMR) or ESD at the initial intervention, if necessary to completely resect an area of superficial tumor or mucosal nodularity less than or equal to 2 cm in maximal dimension."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
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 2016 (unknown)

NCT: national clinical trial.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References

1. Bhat S, Coleman HG, Yousef F et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J. Natl. Cancer Inst. Jul 6 2011; 103(13):1049-1057.
2. Hvid-Jensen F, Pedersen L, Drewes AM et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N. Engl. J. Med. Oct 13 2011; 365(15):1375-1383.
3. Ell C, May A, Pech O et al. Curative endoscopic resection of early esophageal adenocarcinoma (Barrett's cancer). Gastrointest. Endosc. Jan 2007; 65(1):3-10.
4. Pech O, Ell C. Endoscopic therapy of Barrett's esophagus. Curr Opin Gastroenterol. Sep 2009; 25(5):405-411.
5. Overholt BF, Lightdale CJ, Wang KK et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc. Oct 2005; 62(4):488-498.
6. Ganz RA, Overholt BF, Sharma VK et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc. Jul 2008; 68(1): 35- 40.
7. U.S. Food and Drug Administration. 510(k) Premarket Notification Database: BARRX MODELS HALO360 AND HALO360+ COAGULATION CAT. No. K080557. 2008; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k080557. Accessed October 25, 2017.
8. U.S. Food and Drug Administration. 510(k) Safety Summary: CryoSpray Ablation System. No. K072651. 2007; http://www.accessdata.fda.gov/cdrh_docs/pdf7/K072651.pdf. Accessed

October 25, 2017.

9. U.S. Food and Drug Administration. 510(k) Premarket Notification to Check-Med Systems, Inc. 2002; https://www.accessdata.fda.gov/cdrh_docs/pdf2/k021387.pdf. Accessed November 16, 2017

10. Hernandez JC, Reicher S, Chung D et al. Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia. Endoscopy May 2008; 40(5):388-392.

11. Pouw RE, Gondrie JJ, Sondermeijer CM et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. J Gastrointest Surg. Oct 2008; 12(10):1627-1636; discussion 1636-1627.

12. Roorda AK, Marcus SN, Triadafilopoulos G. Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia. Dis Esophagus. 2007; 20(6):516-522.

13. Sharma VK, Wang KK, Overholt BF et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc. Feb 2007; 65(2):185-195.

14. Chadwick G, Groene O, Markar SR et al. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointest Endosc. May 2014;79(5):718-731 e713.

15. van Vilsteren FG, Pouw RE, Seewald S et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut. Jun 2011; 60(6):765-773.

16. Shaheen NJ, Sharma P, Overholt BF et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. May 28 2009; 360(22):2277-2288.

17. Shaheen NJ, Overholt BF, Sampliner RE et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. Aug 2011; 141(2):460-468.

18. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. Oct 2013; 11(10):1245-1255.

19. Semlitsch T, Jeitler K, Schoefl R et al. A systematic review of the evidence for radiofrequency ablation for Barrett's esophagus. Surg Endosc. Dec 2010; 24(12):2935-2943.

20. Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut. April 2016; 65(4):555-562.

21. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Radiofrequency ablation of nondysplastic or low-grade dysplastic Barrett's esophagus. TEC Assessments. 2010; Volume 25: Tab 5.

22. Eloubeidi MA, Wallace MB, Hoffman BJ et al. Predictors of survival for esophageal cancer patients with and without celiac axis lymphadenopathy: impact of staging endosonography. Ann Thorac Surg. Jul 2001; 72(1):212-219; discussion 219-220.

23. Barret M, Belghazi K, Weusten BL, et al. Single-session endoscopic resection and focal radiofrequency ablation for short-segment Barrett's esophagus with early neoplasia. Gastrointest Endosc. Jul 2016;84(1):29-36.

24. Almond LM, Hodson J, Barr H. Meta-analysis of endoscopic therapy for low-grade dysplasia in

Barrett's oesophagus. Br J Surg. Sep 2014;101(10):1187-1195.

25. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. Mar 26 2014;311(12):1209-1217.

26. Downs-Kelly E, Mendelin JE, Bennett AE et al. Poor interobserver agreement in the distinction of high-grade dysplasia and adenocarcinoma in pretreatment Barrett's esophagus biopsies. Am J Gastroenterol. Sep 2008; 103(9):2333-2340; quiz 2341.

27. Yerian L. Histology of metaplasia and dysplasia in Barrett's esophagus. Surg Oncol Clin N Am. Jul 2009; 18(3):411-422.

28. Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol. Mar 2008; 103(3):788-797.

29. Kerkhof M, van Dekken H, Steyerberg EW, et al. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. Histopathology. Jun 2007;50(7):920-927.

30. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. Jul 2010;105(7):1523-1530.

31. Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. May 2015;64(5):700-706.

32. Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc. Nov 2008; 68(5):867-876.

33. Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy. Oct 2010; 42(10):781-789.

34. Ertan A, Zaheer I, Correa AM et al. Photodynamic therapy vs radiofrequency ablation for Barrett's dysplasia: efficacy, safety and cost-comparison. World J Gastroenterol. Nov 7 2013; 19(41):7106-7113.

35. David WJ, Qumseya BJ, Qumsiyeh Y, et al. Comparison of endoscopic treatment modalities for Barrett's neoplasia. Gastrointest Endosc. Nov 2015;82(5):793-803 e793.

36. Johnston MH, Eastone JA, Horwhat JD et al. Cryoablation of Barrett's esophagus: a pilot study. Gastrointest Endosc. Dec 2005; 62(6):842-848.

37. Dumot JA, Vargo JJ, Falk GW et al. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc. Oct 2009; 70(4):635-644.

38. Greenwald BD, Dumot JA, Horwhat JD et al. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus. Jan 2010; 23(1):13-19.

39. Shaheen NJ, Greenwald BD, Peery AF et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc. Apr 2010; 71(4):680-685.

40. Canto MI, Shin EJ, Khashab MA, et al. Safety and efficacy of carbon dioxide cryotherapy for treatment of neoplastic Barrett's esophagus. Endoscopy. Jul 2015;47(7):582-591.

41. Sengupta N, Ketwaroo GA, Bak DM, et al. Salvage cryotherapy after failed radiofrequency

ablation for Barrett's esophagus-related dysplasia is safe and effective. Gastrointest Endosc. Sep 2015;82(3):443-448.

42. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. Jan 2016;111(1):30-50; quiz 51.

43. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. Jan 2014;63(1):7-42.

44. SGE Standards of Practice Committee, Evans JA, Early DS, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. Dec 2012;76(6):1087-1094.

45. Sharma P, Katzka DA, Gupta N, et al. Quality Indicators for the Management of Barrett's Esophagus, Dysplasia, and Esophageal Adenocarcinoma: International Consensus Recommendations from the American Gastroenterological Association Symposium. Gastroenterology. Nov 2015;149(6):1599-1606.

46. Spechler SJ, Sharma P, Souza RF et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. Mar 2011; 140(3):1084-1091.

47. Stefanidis D, Hope WW, Kohn GP et al. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc. Nov 2010; 24(11):2647-2669.

48. Network NCCN. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophogastric Junction Cancers Version 3.2015: http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf. Accessed September 15, 2017.

49. Blue Cross Blue Shield Association. Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus. Medical Policy Reference Manual. 2.01.80. Revised November 2017.