

Protocol

Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

(20180)

Medical Benefit		Effective Date: 01/01/16	Next Review Date: 09/20
Preauthorization	No	Review Dates: 05/09, 03/10, 03/11, 03/12, 07/12, 03/13, 03/14, 09/14, 09/15, 09/16, 09/17, 09/18, 09/19	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With Barrett esophagus with high-grade dysplasia 	Interventions of interest are: <ul style="list-style-type: none"> Endoscopic radiofrequency ablation 	Comparators of interest are: <ul style="list-style-type: none"> Esophagectomy Endoscopic mucosal resection Surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Barrett esophagus with low-grade dysplasia 	Interventions of interest are: <ul style="list-style-type: none"> Endoscopic radiofrequency ablation 	Comparators of interest are: <ul style="list-style-type: none"> Surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Barrett esophagus without dysplasia 	Interventions of interest are: <ul style="list-style-type: none"> Endoscopic radiofrequency ablation 	Comparators of interest are: <ul style="list-style-type: none"> Surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Barrett esophagus with or without dysplasia 	Interventions of interest are: <ul style="list-style-type: none"> Endoscopic cryoablation 	Comparators of interest are: <ul style="list-style-type: none"> Esophagectomy Endoscopic mucosal resection Surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity

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.

SUMMARY OF EVIDENCE

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 one 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 two 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.

Clinical input was obtained in 2012, and it 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.

POLICY

Radiofrequency ablation may be considered **medically necessary** for the treatment of Barrett esophagus with high-grade dysplasia (see Policy Guidelines).

Radiofrequency ablation may be considered **medically necessary** for the treatment of Barrett esophagus with low-grade dysplasia, when the initial diagnosis of low-grade dysplasia is confirmed by two physicians (see Policy Guidelines).

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

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

POLICY GUIDELINES

RFA for Barrett esophagus with HGD may be used in combination with endoscopic mucosal resection of nodular or visible lesions. The diagnosis of HGD should be confirmed by two pathologists before initiating RFA.

There is considerable interobserver variability in the diagnosis of 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 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 as achieved using two expert pathologists (Kerkhof et al, 2007).

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 biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, which is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, resulting in the phenotypic expression of histologic features from LGD, to 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 8,000 patients with a mean duration of follow-up of seven years (range, one to 20 years).¹ The de novo progression to cancer from BE at one 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%.² Detection of LGD on index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1,000 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.^{3,4} 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.⁵

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.⁶ Kerkhof et al (2007) reported that, in patients with an initial pathologic diagnosis of LGD, review by an expert pathologist would result in the initial diagnosis being downgraded to nondysplasia in up to 50% of cases.⁷ Curvers et al (2010) tested this hypothesis in 147 patients with BE who were given an initial diagnosis of LGD.⁸ All pathology slides were read by two 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.⁹ 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 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.¹⁰ In this sample, 73% of subjects were downstaged.

Management

The management of BE includes 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).¹¹ The five 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%.¹²

Ablative 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, 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.¹³ (Photodynamic therapy for BE is discussed in the Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus Protocol.)

The CryoSpray Ablation system uses a low-pressure spray for applying liquid nitrogen through an upper endoscope. Cryotherapy allows for 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 two components: an energy generator and an ablation catheter. The generator provides rapid (i.e., less than one second) delivery of a predetermined amount of radiofrequency energy to the catheter. 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 three 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 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%.¹⁴ Another potential advantage to 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 under treatment for approximately 10% of patients with undetected submucosal cancer, in whom esophagectomy would have been required.¹²

REGULATORY STATUS

In 2005, the HALO360 (now Barrx™ 360 RFA Balloon Catheter; Barrx Medical; acquired by Covidien in 2012) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process and, in 2006, the HALO90 (now Barrx™ 90 RFA Focal Catheter) received clearance. FDA-labeled indications are for use in coagulation of bleeding and nonbleeding sites in the gastrointestinal tract and include the treatment of BE.¹⁵ FDA product code: GEI.

In 2007, the CryoSpray Ablation™ System (formerly the SprayGenix Cryo Ablation system; CSA Medical) 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.”¹⁶ 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 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.”¹⁷

RELATED PROTOCOLS

Confocal Laser Endomicroscopy

Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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