

RADIOFREQUENCY ABLATION AS A TREATMENT OF DYSPLASTIC BARRETT'S ESOPHAGUS

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) has been asked to review the scientific literature on the safety and efficacy of radiofrequency ablation (RFA) for the treatment of dysplastic Barrett's esophagus because of the publication of a recent new clinical trial comparing radiofrequency ablation with a sham procedure.

CTAF has previously reviewed the literature on the safety and efficacy of photodynamic therapy for high grade esophageal dysplasia, but has not previously reviewed the literature for the use of RFA for the treatment of high grade esophageal dysplasia.

BACKGROUND

Barrett's Esophagus and Dysplasia

Barrett's esophagus (BE) is defined as a pre-malignant lesion where the normal squamous epithelium that lines the esophagus is replaced by columnar epithelium similar to that in the lining of the intestines. It is detected in the majority of patients with esophageal and gastroesophageal adenocarcinomas. The five year survival rate for these cancers is low (15-20%)¹. In the U.S. it was estimated that in 2009, 16,400 new cases of esophageal cancer would be diagnosed and that about 60% would be adenocarcinomas². The risk for esophageal cancer among patients with BE is about 30-40 times higher than in those without it.

The progression of BE starts with nondysplastic intestinal metaplasia which can include low grade dysplasia (LGD) and high grade dysplasia (HGD) before the development of cancer. Most cases of BE do not progress beyond nondysplastic intestinal metaplasia or transient LGD^{3,4}. Many cases of LGD will regress on their own. In a prospective study of 1,376 patients, 66% with LGD had regression to no dysplasia³.

The biggest risk factors for progression to cancer are the length of the abnormal mucosa and the degree of dysplasia⁵⁻⁷. Among patients with BE but without dysplasia, the risk of esophageal adenocarcinoma is approximately 0.5% per year. Among patients with LGD, the risk is approximately 0.6% per year⁸. Among

those cases that do progress to HGD, the risk of esophageal cancer may be anywhere from 4% to more than 10% per patient year^{9 10-12}.

Risk factors for the development of BE include advancing age, male sex, white race, symptoms of reflux and obesity^{13, 14}.

Screening for BE among patients with chronic reflux is recommended by some gastrointestinal (GI) societies¹⁵⁻¹⁷ but is controversial. Many individuals who develop esophageal adenocarcinoma had no prior symptoms of reflux¹⁸, and BE can occur in the absence of symptoms of chronic reflux¹⁹.

Treatment of Neoplastic Barrett's Esophagus

For individuals with HGD, there are generally four possible management options:

- 1) esophagectomy
- 2) endoscopic therapies that ablate the neoplastic tissue
- 3) endoscopic mucosal resection
- 4) intensive esophageal surveillance where invasive therapies are withheld until biopsy specimens reveal adenocarcinoma

For individuals with LGD, whose risk of progressing to cancer is lower, the management options typically include either intensive surveillance or one of the ablative therapies.

There are risks and benefits with each of the four approaches. In addition, the follow-up has typically been less than five years and so the effect of the various strategies on cancer mortality is not known.

Esophagectomy: Esophagectomy has typically been the main treatment in patients with HGD, because of the concern for a high rate (up to 40%²⁰) of coexisting esophageal adenocarcinoma. However, a recent systematic review showed that among patients undergoing esophagectomy for HGD, the prevalence of invasive cancer was 12.7%; when there were no abnormal lesions visualized during endoscopy, the prevalence was only 3%²¹. In addition, esophagectomy is associated with substantial morbidity and mortality. Complications occur in 30-50% of patients including cardiac complications, pneumonia and anastomotic leak or stricture and the mortality rate is 1-5%^{22, 23}. Because of this, attention has turned toward less invasive treatment strategies.

Endoscopic Mucosal Resection: Multimodal endoscopic eradication therapy includes removing visible neoplastic lesions by endoscopic mucosal resection and then eradicating the remaining metaplastic epithelium with one of several different ablative techniques. These techniques include photodynamic therapy, RFA, cryoablation and argon plasma coagulation²⁴.

Ablative Therapies: The goal of the endoscopic ablative therapies is to ablate the abnormal epithelium of BE. Different types of energy (thermal, photochemical or radiofrequency) are used to ablate the abnormal tissue. After the ablation is complete, proton pump inhibitors are given so that the injured epithelium heals with the development of new squamous epithelium. A potential concern with the ablative therapies is that all the dysplastic tissue may not be eradicated. Metaplastic mucosa that is partially ablated can then become buried by the new squamous tissue and can develop into a new adenocarcinoma²⁵.

Radiofrequency ablation (RFA): RFA ablates BE using radiofrequency energy. The radiofrequency energy can either be delivered circumferentially or focally. There are two different devices and accessories, both manufactured by BARRX. The balloon based HALO³⁶⁰ device is used to treat circumferential areas of BE. The system includes a high-power energy generator, a sizing balloon catheter and several balloon based ablation catheters. There are 60 tightly spaced, bipolar independent electrodes encircling the balloon through which the energy is delivered. A preselected amount of energy is delivered in less than a second at 350 W. This allows for full thickness ablation of the epithelium without damage to the submucosa^{26, 27}. The HALO⁹⁰ ablation system is used to treat more focal areas and uses a radiofrequency generator and an endoscope mounted electrode. Both procedures can be done on an outpatient basis.

In conclusion, RFA is proposed as an alternative to esophagectomy or endomucosal resection for the treatment of high grade esophageal dysplasia. The theoretic advantages are that it can be done as an outpatient, and may have a lower rate of complications than esophagectomy.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: **The technology must have final approval from the appropriate government regulatory bodies.**

The HALO Coagulation Systems (BARRX Medical, Inc., Sunnyvale, CA) have received FDA 510(k) clearance: HALO³⁶⁰ in 2005, the HALO⁹⁰ in 2006, and most recently, HALO^{FLEX} in 2009.

These devices were approved for use (per the FDA) in the coagulation of bleeding and non-bleeding sites in the gastrointestinal tract including but not limited to the esophagus. Indications include Esophageal Ulcers, Mallory-Weiss tears, Arteriovenous Malformations, Angiomata, Barrett's esophagus, Dieullafoy Lesions, and Angiodysplasia. In addition the HALO^{FLEX} is indicated for use for the coagulation of soft tissue.

TA Criterion 1 is met

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

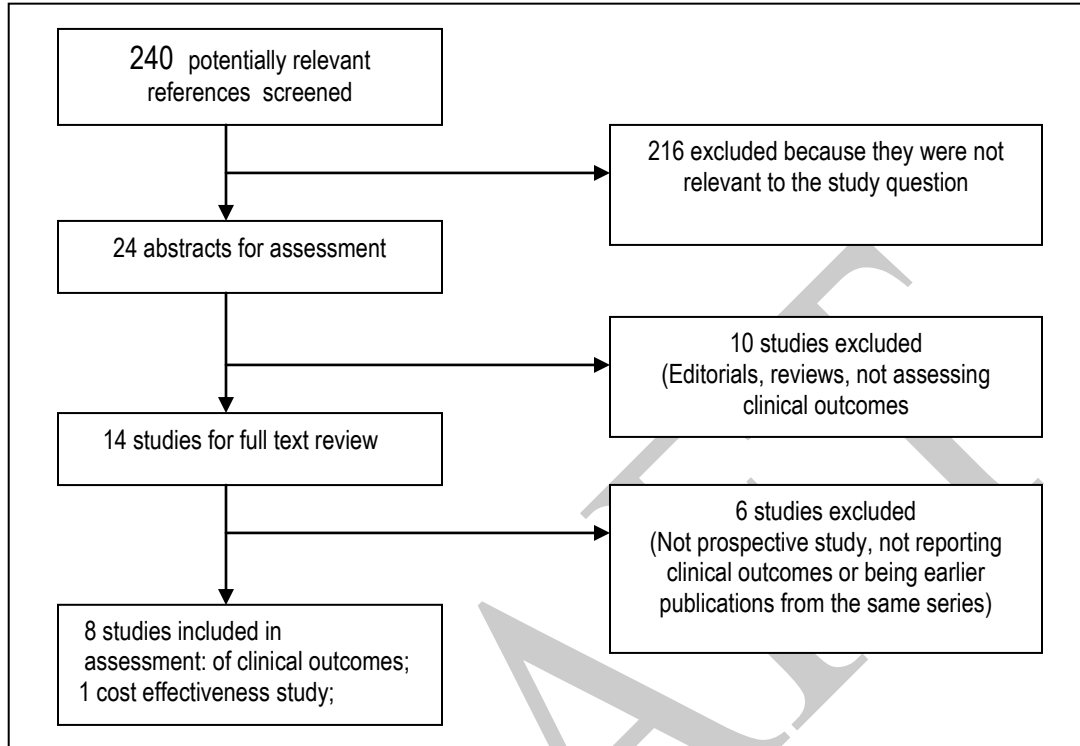
The Medline database, EMBASE, Cochrane clinical trials database, Cochrane reviews database and Database of Abstracts of Reviews of Effects (DARE) were searched using the key words radiofrequency ablation therapy or RFA or radio wave or catheter ablation, OR endoscopic, also with the terms Barrett's esophagus and dysplasia and human. The search was performed for the period from 1966 to January, 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturer. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Inclusion criteria:

- Study had to evaluate the efficacy of radiofrequency ablation in the treatment of dysplastic Barrett's esophagus
- Study had to be prospective
- Study had to measure clinical outcomes
- Included only humans
- Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes or if they were retrospective and/or if they were case series.

Figure 1: Selection of studies for inclusion in review



A total of 240 potentially relevant articles were identified. 216 were excluded for not addressing the research question. A total of 24 studies were evaluated. 16 were excluded. Reasons for exclusion included not being a prospective study, not reporting clinical outcomes or being earlier publications from the same series.

We identified six prospective studies, one U.S. registry and one published clinical trial evaluating the efficacy of RFA for the treatment of dysplastic BE and one cost effectiveness study. Subsequently, a second U.S. registry publication that was an in-press article was identified.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

The main goal of treating any pre-cancerous lesion or condition is to reduce subsequent cancer mortality. Esophageal cancer has a high five year mortality rate and so any efforts to reduce that are important. The

primary potential advantage of RFA would be preventing the development of esophageal cancer in patients with HGD, while avoiding the morbidity and mortality associated the standard treatment, esophagectomy.

Prospective Studies

A total of six prospective uncontrolled studies of the effect of RFA on clinical outcomes in the treatment of dysplastic BE have been published (Table 1). These six studies have included a total of 137 patients. In most of the studies, patients first received circumferential ablation and then subsequently received focal ablation later in the study if necessary. The outcomes were usually complete eradication of dysplasia or complete eradication of metaplasia.

Most of these studies have been small (including 10-24 patients) although one included 70 patients. Length of follow-up has ranged from 12 months to 2 1/2 years. Overall, there has been at least a 70% complete resolution of metaplasia or dysplasia in most of the studies (Table 2) In the largest of these studies, 70 patients with intestinal metaplasia but without dysplasia were treated with circumferential ablation with the addition of focal ablation, and were followed for an average of two and a half years. At 12 months, 70% of patients had complete remission of intestinal metaplasia. At 30 months after additional focal therapy, 98% of evaluable patients had a complete remission of intestinal metaplasia. There were no strictures or buried glands. Although this study and the other prospective studies showed that the technology was promising, the lack of a control group and the short duration of follow-up are important limitations.

Table 1: Prospective Studies of Radiofrequency Ablation for the Treatment of Dysplastic Barrett's Esophagus

Author	N	Treatment	Inclusion Criteria	Length of follow-up	Outcomes Evaluated
Shaheen, 2009 ²⁸	127	RFA (up to 4 ablation sessions) vs. sham	Age 18-80 Endoscopically evident non-nodular, dysplastic BE of no more than 8 cm EMR permissible 8 weeks or more before study entry	12 months	<p>Primary</p> <ul style="list-style-type: none"> Proportion of patients with low grade dysplasia who had complete eradication of dysplasia at 12 months Proportion of patients with high grade dysplasia who had complete eradication of dysplasia at 12 months Proportion of all patients who had complete eradication of intestinal metaplasia at 12 months <p>Secondary</p> <ul style="list-style-type: none"> Proportion with progression of dysplasia Proportion free from intestinal metaplasia at 12 months Adverse events Discomfort
Gondrie, 2008a ²⁹	11	Stepwise circumferential and focal ablation (focal ablation became available midway through the study period)	Age 18-85 Intestinal metaplasia 2-10 cm	14 months	<p>Primary</p> <ul style="list-style-type: none"> CR-dysplasia CR-intestinal metaplasia <p>Secondary</p> <ul style="list-style-type: none"> Complications Symptoms

Gondrie, 2008b ³⁰	12	Stepwise circumferential and focal ablation	Age 18-85 Intestinal metaplasia on biopsy 2-10 cm	14 months	CR-dysplasia CR-intestinal metaplasia
Pouw, 2009 ³¹	24	RFA in conjunction with EMR	Age 18-85 BE length of 12 cm or less HGIN or EC in BE segment on two endoscopies Visible lesions removed before RFA No evidence metastatic disease	Median 22 months 6 months (n=23) 12 months (n=13) 24 months (n=8)	Complete response: all biopsies negative for intestinal metaplasia Secondary outcomes: disease progression, adverse events and durability of complete response
Fleischer, 2008 ³²	70	Circumferential ablation with the addition of focal ablation	18-75 IM without dysplasia 2-6 cm BE segment	2.5 years	Complete absence of IM in each patient from biopsies at 12 and 30 months Secondary outcomes: Adverse Events
Sharma, 2009 ³³	62	Circumferential ablation with the addition of focal ablation	18 years and older Low grade dysplasia	24 months	Complete response dysplasia Complete response intestinal metaplasia
Hernandez, 2008 ³⁴	10	Circumferential ablation with the addition of focal ablation	2-6 cm BE segment	12 months	CR-intestinal metaplasia Complications

Complete response defined as “all biopsies negative for dysplasia or intestinal metaplasia”

Table 2: Summary of Results from Prospective Studies of Radiofrequency Ablation for Treatment of Barrett’s Esophagus

Study	N	Type	Results
Shaheen, 2009 ²⁸	127	Trial RFA vs. Sham	Low grade dysplasia group: complete eradication in 90.5% vs. 22.7% in control group (P<0.001) High grade dysplasia group: complete eradication in 81% vs. 19% in control group (p<0.001) Overall: 77.4% vs. 2.3% in control group (p<0.001)
Gondrie, 2008a	11	Prospective cohort	100% CR-IM 100% CR-dysplasia at 14 months
Gondrie, 2008b	12	Prospective cohort	100% CR-dysplasia 100% CR-IM at 14 months
Pouw, 2009 ³¹	24	Prospective cohort	95% eradication of neoplasia 88% eradication of intestinal metaplasia
Fleischer, 2008 ³²	70	Prospective Uncontrolled trial	70% CR-IM at 12 months 98% CR-IM at 30 months after additional focal therapy
Sharma, 2009 ³³	62	Prospective	89% CR- dysplasia at 24 months 79% CR-intestinal metaplasia at 24 months
Hernandez, 2008 ³⁴	10	Prospective Pilot	70% CR-IM No major complications

Randomized Controlled Trials (RCTs)

In the recent multi-center industry sponsored study by Shaheen et al²⁸, RFA was compared with a sham procedure. Patients with dysplastic BE were assigned to either receive RFA or a sham procedure. Randomization was stratified by degree of dysplasia and the length of BE. The primary outcomes were complete eradication of dysplasia and complete eradication of intestinal metaplasia; these outcomes were evaluated at 12 months. Patients in the ablation group could receive up to four ablation sessions that were performed at baseline and at two, four and nine months. The ablation was initially circumferential, and then if needed, focal ablation was done. Patients with LGD underwent endoscopic biopsies at six and 12 months and patients with HGD underwent endoscopic biopsies at baseline, two, four and nine months. Outcomes were assessed separately in the low grade and high grade dysplasia groups. Among those with LGD, complete eradication of dysplasia occurred in 90.5% of those in the ablation group compared with 22.7% of those in the control group (p, 0.001). Among those with HGD, there was 81% complete eradication of dysplasia in the treatment group, compared with 19% of those in the control group (p, 0.001). Overall, complete eradication of metaplasia was 77.4% versus 2.3% of those in the control group (P<0.001). Although cancer incidence was not the primary outcome and there were relatively few cancers, cancer incidence was lower in the ablation group than in the control group (1.2% vs. 9.3%; p=0.045).

Risks/Harms

The major potential harms are the formation of esophageal strictures after the procedure, post procedure complications such as chest pain and the potential for buried metaplasia.

In the RCT by Shaheen et al, there were more adverse events in the ablation group; chest pain scores as rated by a visual analogue scale were higher in the RFA group. Five patients in the RFA group (6%) developed esophageal strictures after the procedure. However, the rate of subsquamous intestinal metaplasia was significantly lower in the RFA group than in the control group (5.1% vs. 40.0%; P<0.001)²⁸.

Accurate complication rates are hard to calculate in the small prospective studies, but in the one prospective study with 70 patients, there were no esophageal strictures or buried metaplasia seen at 12 or 20 month follow-up³².

In two published registry studies, which followed patients who had received RFA for dysplastic BE, esophageal stricture was also rare. In the first, 142 patients, who had received RFA in 16 academic and community centers, were followed for a median of 12 months. There was one asymptomatic stricture and no buried glands. In the second study, 429 patients from four community based practices were followed for a median of 20 months, a stricture occurred in 2.1% of patients and there were no serious procedure related events. In addition, no buried glands were identified³⁵.

Thus, the short term risks of RFA appear to be relatively few, but since the studies only followed participants up to 20 months, longer term safety is not known.

Cost-Effectiveness Analyses

Inadomi and colleagues conducted a cost-utility analysis of the use of ablative therapy for patients with BE. The goal was to compare ablative therapy with endoscopic surveillance. They conducted separate analyses for those with no dysplasia, those with LGD and those with HGD. Several strategies were compared, including no endoscopic surveillance, endoscopic surveillance with ablation for new dysplasia, immediate ablation followed by surveillance for all patients in all patients or limited to patients in whom metaplasia persisted or esophagectomy. In addition to RFA, other ablation techniques that were included were photodynamic therapy, argon plasma coagulation and multipolar electrocoagulation. For patients with HGD, they found that ablation could increase life expectancy by three quality adjusted life years at a cost of less than \$6,000 compared with no intervention. For individuals with LGD, ablation could be effective but if continued surveillance was required, it would be very expensive. A very important question which drives the cost-effectiveness for patients with LGD is whether or not patients who have undergone ablation need continued endoscopic surveillance or whether they can be presumed to be normal after the ablation is complete. It is currently not known how many of these patients will ultimately progress to cancer over the longer term given that the study follow-up to date has been relatively short³⁶.

In summary, RFA in patients with dysplastic BE can achieve high rates of complete remission of metaplasia and dysplasia and appears to be safe at least in the short term. In addition, cancer incidence was lower in the treated group than in the sham group in the one RCT of the technology. At least in the short term, RFA appears to improve net health outcomes.

TA Criterion 3 is met

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The majority of studies of RFA were either pilot studies or uncontrolled studies. Only one study has compared RFA to any other treatment. In the recent multi-center industry sponsored study described above by Shaheen et al²⁸, RFA was compared with a sham procedure. Although RFA was significantly better than the sham procedure in achieving complete eradication of dysplasia both in patient with high grade and with LGD, and even showed a lower incidence of cancer, the study did not show how RFA would directly compare with any of the established management options which would include intensive surveillance or esophagectomy for those with HGD and intensive surveillance for those with LGD.

The risks and benefits differ for high grade and low grade dysplasia. For HGD, the risk for progression to cancer is significantly higher than for LGD. Among individuals with HGD, how does RFA compare with esophagectomy or intensive surveillance? These strategies have not been compared directly, however, historical data show that esophagectomy has a mortality rate of 3-5%, a complication rate of 40-50% and a risk of permanent loss of function of the esophagus³⁷ whereas RFA, which can be done as an outpatient, has a low complication rate and can successfully eradicate the majority of HGD, seems to be a very attractive alternative. Intensive surveillance to determine when a cancer develops is another option for HGD, but with high grade dysplasia, there is a significant risk of progression to cancer and then when the cancer does develop, the individual would require invasive treatment of that cancer, such as esophagectomy with the associated risks and complications.

Among individuals with LGD, the relevant clinical question is how RFA compares with intensive endoscopic surveillance. Since not all LGD will progress to cancer, and since some LGD will regress on its own, treatment of all LGD may not be warranted. In the Shaheen RCT, where RFA was compared

to a sham procedure, an important question is what percentage of those with LGD treated with RFA versus those who received the sham procedure will ultimately progress to cancer? In this study, since control group individuals had the option to receive RFA treatment after the study was over, the answer to this question will not be known. With endoscopic surveillance, low grade lesions can be followed and if they develop into HGD can be treated then. No study has yet compared RFA with intensive endoscopic surveillance in patients with LGD.

Many unanswered questions do still remain- will the complete response seen with ablation persist over time? What are the long term effects of RFA?

In summary, in patients with HGD, although the alternatives of RFA, intensive endoscopic surveillance and esophagectomy have not been compared directly, because none of the established alternatives are really ideal, RFA appears to be at least as beneficial as the established alternatives for individuals with BE with HGD.

In patients with LGD, the established alternative is intensive endoscopic surveillance. Since many LGD lesions will not progress to cancer and may actually regress, intensive endoscopic surveillance with treatment of HGD lesions, should they develop, is a potential alternative. A clinical trial is needed to compare RFA with intensive endoscopic surveillance in individuals with BE and LGD.

TA criterion 4 is met for individuals with BE and HGD

TA Criterion 4 is not met for individuals with BE and LGD

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, one randomized multi-center clinical trial has compared RFA for BE with Dysplasia with a sham procedure. RFA has not been compared with any other treatment in the investigational setting.

There was a multi-center U.S. registry study published in which 142 patients who had BE with HGD from 16 academic and community centers were followed for a median of 12 months. In this registry, no serious adverse events were reported- there was one asymptomatic stricture and no buried glands.

In a second registry study, 429 patients with metaplasia with or without dysplasia who had RFA procedures in community practice settings were followed for a median of nine months. Although these results are promising, there was no comparison group and the follow-up was relatively short.

In conclusion, two registry studies have shown RFA appears to have similar safety and efficacy when done in the community as that seen in the investigational setting. The follow-up for all the studies is relatively short, however for individuals with HGD, for whom the main management alternatives are either esophagectomy or intensive endoscopic surveillance with invasive therapies when cancer is found, the results seen with RFA can be expected to be comparable to those seen in investigational settings.

For patients with LGD, since an improvement in clinical outcomes compared with other treatments has not yet been demonstrated in the investigational setting, it cannot be attained outside the investigational setting.

TA criterion 5 is met for individuals with BE and HGD

TA Criterion 5 is not met for individuals with BE and LGD

CONCLUSION

In summary, dysplastic BE can progress to esophageal cancer and the risk of progression is different for low grade versus high grade dysplasia. RFA as a treatment option can lead to a complete remission of dysplasia in a majority of patients over short term follow-up. When compared with a sham procedure, rates of complete resolution of dysplasia are significantly lower among treated individuals with either HGD or LGD. Although RFA has not been directly compared with other treatment alternatives, the currently available treatment options for individuals with HGD, which include esophagectomy or intensive endoscopic surveillance with invasive therapy once cancer is found are not ideal and have significant complication rates.

For individuals with LGD, many of the LGD lesions will regress on their own so it is less clear that they all need to be treated. The main management options are intensive endoscopic surveillance (with



subsequent treatment of the HGD should it develop) or ablative therapy, such as RFA. A clinical trial is needed to compare these two strategies in patients with LGD.

DRAFT RECOMMENDATION

- RFA for the treatment of BE meets CTAF Criteria 1-5 for the treatment of individuals with HGD.
- RFA for the treatment of BE does not meet CTAF Criteria 4-5 for the treatment of individuals with LGD.

February 17, 2010

This is the first assessment of this technology by CTAF.

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RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted an assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

A search of the CMS web site resulted in the determination that neither an NCD nor an LCD has been developed for the use of this technology.

American Gastroenterological Association (AGA)

The AGA has provided an opinion regarding the use of this technology. A representative will attend the meeting to provide testimony.

American Society of Gastrointestinal Endoscopy (ASGE)

The ASGE has provided an opinion regarding the use of this technology. A representative has been invited to provide testimony at the meeting.

Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

SAGES is currently in the process of updating their guidelines. A representative will not be attending the meeting.

American College of Gastroenterology (ACG)

The ACG has provided opinion regarding the use of this technology. A representative has been invited to provide testimony at the meeting.

American Cancer Society (ACS)

The ACS does not currently have an opinion regarding the use of this technology. The absence of ACS comments reflects neither favorably or unfavorably on this procedure. A representative will not be attending the meeting.

Association of Northern California Oncologists (ANCO)

ANCO has been invited to provide an opinion regarding this technology and to have a representative participate at the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC has been invited to provide an opinion regarding this technology and to have a representative participate at the meeting.

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines do not address the use of this technology.

DRAFT

ABBREVIATIONS USED IN THIS REVIEW

CTAF	California Technology Assessment Forum
RFA	Radiofrequency ablation
BE	Barrett's esophagus
LGD	Low grade dysplasia
HGD	High grade dysplasia
GI	Gastrointestinal
DARE	Database of Abstracts of Reviews of Effects
EMR	Endoscopic mucosal resection
CR-D	Complete resolution-dysplasia
CR-IM	Complete resolution-intestinal metaplasia
HGIN	High grade intraepithelial neoplasia
EC	Early cancer
RCT	Randomized controlled trial

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