Clinical Review Criteria

Photodynamic Therapy (PDT) for Advanced Esophageal Cancer and Barrett’s Esophageal Disease

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Criteria
See main photodynamic therapy criteria document.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background
Esophageal carcinoma is the seventh most common malignancy worldwide. Its incidence is increasing rapidly in the western world mainly due to adenocarcinoma of the lower third of the esophagus and gastro-esophageal junction, which usually arises from areas of Barrett’s metaplasia (Lee 2001). Approximately 13,100 new cases of adenocarcinoma were diagnosed in the United States in 2002. The overall survival rate from esophageal cancer is 5-10% (Litle 2003). Most patients present with dysphagia, which usually occurs at an advanced stage of the disease. At that time, the lumen of the esophagus is often reduced by at least 50% of its diameter among most of the patients.

Radical esophageal resection is still considered the therapeutic gold standard in patients with high-grade dysplasia or early cancer. For those not legible for surgical resection, treatment is palliative to reduce the esophageal obstruction and reduce the dysphagia. Different forms of palliative treatment include: external beam radiation therapy, brachytherapy, pneumatic dilatation, esophageal stenting, Nd: YAG laser, and photodynamic (PDT) therapy. Some of these therapies e.g. external radiation therapy may take several weeks to relieve the dysphagia, others like esophageal bypass have a longer recovery time, and still others are associated with severe side effects as stricture, perforation, reflux, fistula formation and others.

PDT is a two-part treatment using a photosensitizing drug, and red non-thermal laser light (green light has been used in some studies). The photosensitizing agent is a light- activated chemical that is selectively retained in tumor cells, and interstitial tissue of the tumor. (McCaughan, 1996). This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. For Photofrin, the FDA approved photosensitizer, the wavelength of light used for activation is 630 nm. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the tumor, and result in its necrosis in about 24 to 48 hours. The depth of penetration and tumor necrosis after PDT is limited to approximately 5-10 mm. This shallow depth of light penetration in the tumor provides a safety factor against perforation, but on the other hand it is a limiting factor to the effectiveness of the therapy for deeper tumors.
Photodynamic therapy is an outpatient procedure, performed with the patient sedated. It can be used together with other treatments, and can be repeated several times. It does not require anesthesia or pre-dilation of the esophagus.

Sensitivity of the patient body tissues to light always occurs once the agent is injected, and the patients should avoid direct light for at least four weeks. An important adverse effect of PDT is the potential formation of esophageal strictures due to fibrosis and scarring during the healing process.

Barrett’s esophagus is a condition where the squamous epithelium of the lower esophagus is substituted by specialized columnar mucosa. It is estimated to affect 700,000 adults in the United States (FDA 2003), and is believed to occur as a response to esophageal reflux of gastric contents especially gastric acid. Barrett’s esophagus is regarded as a premalignant condition and is the most important risk factor for the development of adenocarcinoma (Spechler 2002). Non-dysplastic metaplasia can progress to low-grade dysplasia, high-grade dysplasia, and finally to invasive cancer (Conio 2005). Several investigators reported that the relative risk of the adenocarcinoma depends on several negative prognostic factors among which are metaplasia extension, length of the involved segment, dysplasia grading, and timing of diagnosis (Pagoni 2003). Esophageal adenocarcinoma is often diagnosed at an advanced stage of the disease, and thus has a poor prognosis with 5-year survival rates below 20% (Enzinger 2003).

The increased availability of endoscopy and awareness of Barrett’s esophagus and its associated cancer risk, have led to the increased detection of the condition in premalignant or early malignant stages. Partial or total esophagogastrectomy are considered the therapeutic gold standard in patients with high-grade dysplasia or early cancer. Surgical resection may however, be associated with high morbidity and mortality rates especially in low-volume surgical centers (Birkmeyer 2002). Moreover, some patients may be unfit for surgery.

Other possible strategies have been proposed to destroy Barrett’s mucosa. Among these techniques are photodynamic therapy (PDT), ablation therapy with Nd-YAG laser, Argon Plasma Coagulation (APC), and endoscopic mucosal resection (EMR). The objective of all these treatments is the complete destruction of the abnormal mucosa to reduce the cancer risk. The ideal treatment would destroy columnar metaplasia, and achieve regeneration of the squamous epithelium.

PDT is a two-part treatment using a photosensitizing drug and red non-thermal laser light (green light has been used in some studies). The photosensitizing agent is a light- activated chemical that selectively concentrates in malignant tissue. This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the esophageal mucosa in about 24 to 48 hours.

Photodynamic therapy is an outpatient procedure, performed with the patient sedated. It can be used together with other treatments, and may be repeated several times. It does not require anesthesia or pre-dilation of the esophagus.

Sensitivity of the patient body tissues to light always occurs once the agent is injected, and the patients should avoid direct sunlight or any bright light for at least four weeks. An important adverse effect of PDT is the potential formation of esophageal strictures due to fibrosis and scarring during the healing process.

Porfimer sodium (photofrin) was approved by the FDA in December 1995, to use in PDT for the palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with Nd:YAG laser therapy. More recently, in August 2003 it was also approved for the ablation of precancerous lesions in Barrett’s esophagus patients who do not undergo esophagectomy (FDA 2003).
### Medical Director Clinical Review and Policy Committee

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>02/26/04</td>
<td>While there is insufficient evidence of efficacy for treatment of esophageal cancer, the committee did recommend coverage for palliative treatment. However, use of photodynamic therapy in the treatment of Barrett’s Disease is not recommended for coverage at this time.</td>
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<tr>
<td>07/01/05</td>
<td>While there is insufficient evidence of efficacy for treatment for use of photodynamic therapy in the treatment of Barrett’s Disease, the committee recommended delaying decision until 8/8/2005. The committee is requesting feedback from the GI department before making a recommendation.</td>
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<tr>
<td>11/28/05</td>
<td>The committee received feedback from Group Health gastroenterology specialists recommending criteria for coverage. The criteria recommended were approved with minor revisions.</td>
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### Medical Technology Assessment Committee (MTAC)

<table>
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<th>Date</th>
<th>Evidence Conclusion</th>
<th>Outcome</th>
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<tr>
<td>02/06/00</td>
<td>Photodynamic therapy when compared to Nd:YAG thermal ablation for palliation of dysphagia from advanced esophageal cancer provides equivalent improvement in dysphagia, improved objective tumor response as measured by esophageal lumen diameter (ARR of 12% at one month in “complete response + partial response” P &lt;0.05), and increased mild to moderate complications including sunburn in 19% of patients treated with PDT. Perforations from laser treatments or associated dilatations occurred in 1% of patients following PDT and 7% of patients following Nd:YAG treatment. (p&lt;0.05) Termination of laser sessions due to adverse events occurred in 3% of patients receiving PDT and 19% receiving Nd:YAG. While this is an RCT, the high drop out rate and lack of blinding limit our ability to understand the difference in clinically important outcomes between Nd:YAG thermal ablation and PDT.</td>
<td>The use of photodynamic therapy for the treatment of advanced esophageal cancer has been approved by the FDA and therefore meets GHC Medical Technology Assessment Criteria 1. There is insufficient scientific evidence that this treatment is medically effective and therefore GHC criteria 2-5 are not met. In the absence of adequate, well designed studies of effectiveness, the medical appropriateness of this technology (GHC Criteria 6) cannot be determined.</td>
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<tr>
<td>02/11/04</td>
<td>Barrett’s esophagus: Ackroyd’s study was a small RCT with valid methodology. It is randomized, controlled, double blind, and with sufficient power to detect the difference in the treatment response between the two groups despite the small sample size. The trial however compared PDT to placebo and not to an alternative treatment. The photosensitizer used was ALA not the commonly used porphyrin based agent, and the laser light used was the green light, not the red light described in the literature. Effect of the treatment on survival was not studied. Overall the results of the trial show that patients treated with PDT showed significantly more macroscopic and microscopic evidence of regression and reduction in Barrett’s area, compared to those who received a placebo treatment. The response to treatment observed was maintained for the follow-up duration of 24 months. The other study reviewed (Overholt 2003) was a case series with long-term follow-up. The study, like all case series, has potential threats to its internal validity, and lacks a comparison or control group. Its results show that PDT was associated with a success rate (no dysplasia with or without Barrett’s) ranging from 44.4% for cases with early stage carcinoma to 92.9% for cases with low-grade hyperplasia. PDT was not compared to an</td>
<td>The use of photodynamic therapy in treatment of esophageal cancer does not meet the Group Health Medical Technology Assessment Criteria. The use of photodynamic therapy in treatment of Barrett’s disease does not meet the Group Health Medical Technology Assessment Criteria.</td>
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alternative treatment. In addition it was supplemented with Nd: YAG laser photoablation and continuous use of omeprazole, which may be responsible in part for the treatment success.

Advanced esophageal cancer: Only case series data were available. The dysphagia scores seems to significantly improve after PDT treatment in the two series reviewed. There are no studies comparing the PDT with other treatments so the relative effectiveness cannot be determined. Moreover the case series studies are subject to selection and observation bias. A RCT (Lightdale, et al, 1995) with 218 patients randomized to receive either PDT or Nd:YAG was reviewed for MTAC in February 2000. It was not blinded, and had a high dropout rate, and did not provide sufficient evidence to determine the effect of the PDT on the treatment of esophageal cancer.

Conclusion:
- There is some weak evidence from one small RCT that PDT using ALA photosensitizer has more than a placebo effect on the regression of Barrett’s area.
- There is insufficient evidence on the effect of PDT in the palliative treatment of advanced, and/or inoperable esophageal cancer.

06/06/05 Kelty et al’s RCT compared photodynamic therapy (PDT) and argon plasma coagulation (APC) for the ablation of Barrett’s esophagus. The outcomes were the number of treatments required to achieve ablation, and the complete macroscopic reversal of the columnar epithelium. All patients had a biopsy proven Barrett’s epithelium but none had any evidence of dysplasia. Thirty four patients were randomized to each treatment group, and followed for up to two years (range 6-24, median 12 months). 50% of the patients in the PDT group showed complete response to PDT, and 50% had only a partial regression. The APC therapy had significantly better outcomes with a complete response rate of 97%.

Hage et al’s trial was a smaller study (N=40) that also compared PDT with APC, and the primary outcome was the endoscopic reduction of the Barrett’s esophagus surface. All patients had no or a low-grade dysplasia. They were randomized to receive APC therapy, single illumination (PDT 100), or a fractionated illumination (PDT 20+100), and followed for up to two years. The results of the trial show that patients who received a single illumination of PDT had a significantly lower rate of Barrett’s esophagus surface reduction when compared to the PDT 20+100 group or the APC group (51%, 86% and 93% respectively). The difference between the latter two groups was insignificant.

The two studies used 5-aminolevulonic acid (5-ALA); a more recent sensitizing agent and not the FDA approved photofrin (porfimer sodium). Both trials had generally valid methodology. However, they had relatively small sample sizes, and the follow-up duration of 2 years might be insufficient to study the effect of the therapy on reducing the risk of cancer. The outcome in these trials was the effect of the therapy on the reversal of the columnar epithelium and not on patient survival. Moreover, all study subjects had no or low-grade dysplasia, which might limit generalization of the results.

The 2004 MTAC review only found weak evidence from one small RCT that PDT using ALA photosensitizer had more than a placebo effect on the regression of Barrett’s area. The therapy failed the committee evaluation criteria.

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<td>The use of photodynamic therapy in treatment of Barrett’s disease does not meet the Group Health Medical Technology Assessment Criteria.</td>
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In conclusion, the studies reviewed provide some evidence that PDT may achieve complete clearance of Barrett’s epithelium in at least 50% of the patients with no or low-grade dysplasia. They do not provide evidence on the effect of the therapy on higher-grade dysplasia, or its impact on cancer risk, and patient survival. Larger trials with long-term follow-up may be needed to establish these effects.

### Evidence/ Source Documents

<table>
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<tr>
<th>Date of Literature</th>
<th>Articles</th>
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<tr>
<td>2/6/2000</td>
<td>Articles were sorted on the basis of study type. Case series and cohort studies were not selected. Two randomized controlled trials were selected for review. One randomized controlled trial was selected (study by Heier SK et al. <em>Gastroenterology</em>. 1995;109:63-72) was excluded because of small study size: N=44; 20 in PDT group, 22 in Nd:YAG group). An evidence table was created for the best available evidence (Lightdale CJ, et al. <em>Gastrointestinal Endoscopy</em>. 1995;42:507-12.)</td>
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**Reference:**

| 2/11/2004          | Barrett’s esophagus:  
The search revealed 125 articles. The majority were reviews and tutorials. There was one RCT comparing the procedure to placebo, two other small RCTs comparing different methods for performing PDT, and several case series or case reports. The RCT and the case series with a relatively large sample size, and long-term follow-up were selected for critical appraisal.  
Advanced esophageal cancer:  
The search on esophageal cancer in general revealed 94 articles, and that on advanced esophageal cancer revealed 21 articles the great majority of which were review articles. There were no RCTs comparing PTD to other modes of treatment. There were three case series with more than 50 patients each. One of these series compared PDT given in addition to radiotherapy. The other two were critically appraised.  

| 6/6/2005           | The search revealed 26 articles. The majority were review articles or opinion pieces. There were two randomized controlled trials and two case series. The two RCTs were selected for critical appraisal:  
Hage M, Siersema PD, van Dekken H, et al. 5-Aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett’s oesophagus: a randomized trial. *Gut* 2004;53:785-790. See Evidence Table |