Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy Number: 8.01.06  Last Review: 10/2017

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for oncologic applications of photodynamic therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
One or more courses of photodynamic therapy may be considered medically necessary for the following oncologic applications:
- palliative treatment of obstructing esophageal cancer
- palliative treatment of obstructing endobronchial lesions
- treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy
- treatment of high-grade dysplasia in Barrett’s esophagus
- palliative treatment of unresectable cholangiocarcinoma when used with stenting

When Policy Topic is not covered
Other oncologic applications of photodynamic therapy are investigational including, but not limited to, other malignancies and Barrett’s esophagus without associated high-grade dysplasia.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With obstructing</td>
<td>Photodynamic therapy as</td>
<td>Stenting</td>
<td>Change in disease status</td>
</tr>
<tr>
<td>esophageal cancer</td>
<td>palliation</td>
<td>Laser therapy</td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Argon plasma coagulation</td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With obstructing</td>
<td>Stenting</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laser therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Argon plasma coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>endobronchial lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Photodynamic therapy as palliation</td>
<td>Laser therapy</td>
<td>Brachytherapy</td>
<td>External-beam radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in disease status</td>
<td>Symptoms</td>
<td>Quality of life</td>
<td>Treatment-related morbidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy</td>
<td>Photodynamic therapy</td>
<td>Radiofrequency ablation</td>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryotherapy</td>
<td>Disease-specific survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brachytherapy</td>
<td>Change in disease status</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With Barrett esophagus with high-grade dysplasia</td>
<td>Photodynamic therapy</td>
<td>Radiofrequency ablation</td>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryotherapy</td>
<td>Disease-specific survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surveillance</td>
<td>Change in disease status</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esophagectomy</td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cryotherapy</td>
<td>Treatment-related morbidity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With unresectable cholangiocarcinoma</td>
<td>Photodynamic therapy plus stenting as palliation</td>
<td>Stenting alone</td>
<td>Change in disease status</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With other malignancies</td>
<td>Photodynamic therapy</td>
<td>Standard of care</td>
<td>Overall survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease-specific survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change in disease status</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-related morbidity</td>
<td></td>
</tr>
</tbody>
</table>

**Summary**

Photodynamic therapy (PDT; also called phototherapy, photoradiotherapy, photosensitizing therapy, or photochemotherapy) is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance. Treatment for tumor cells occurs through selective retention of the photosensitizing agent and the selective delivery of light.
For individuals who have obstructing esophageal cancer who receive PDT as palliation, the evidence includes systematic reviews, randomized controlled trials (RCTs), and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. A meta-analysis comparing PDT with Nd:YAG laser suggested that improvements in dysphagia are similar, although estimates are imprecise. PDT is associated with a lower risk of perforation compared with Nd:YAG laser treatment; however, PDT runs a higher risk that a patient might react adversely to the light (eg, photosensitivity). PDT plus argon plasma coagulation appears to prolong the time to recurrence of dysphagia as opposed to argon plasma coagulation alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have obstructing endobronchial cancer who receive PDT as palliation, the evidence includes RCTs and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Evidence from RCTs comparing PDT with Nd:YAG laser has generally supported improvements in symptoms with PDT similar to those with laser. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy who receive PDT, the evidence includes uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. There are few patients with early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy; additionally, several treatment methods are available for this population. Studies comparing these treatment methods are not available. Case series of PDT include between 21 and 95 patients and have reported complete response rates ranging from 72% to 100%. Given the small size of this potential population and the ineligibility for standard surgical treatment or radiotherapy, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have Barrett esophagus with high-grade dysplasia who receive PDT, the evidence includes an RCT and observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The RCT compared PDT plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression to cancer persisting during 5 years of follow-up for PDT. The results of the RCT revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Observational comparative data suggested similar mortality outcomes for PDT and esophagectomy over 5 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have unresectable cholangiocarcinoma who receive PDT plus stenting as palliation, the evidence includes systematic reviews, RCTs, and observational studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Two small RCTs and several observational studies have found that PDT plus stenting is associated with greater elimination of bile duct stenosis and improved survival benefit than stenting alone. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival, but not overall survival, with similar rates of adverse events. Case series have suggested an improvement in quality of life with PDT. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small size of this potential population, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other malignancies (eg, gynecologic, bladder, head and neck, brain, soft tissue) who receive PDT, the evidence includes controlled observational studies and uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The published literature on PDT for these malignancies is generally comprised small case series without comparator groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Photodynamic therapy (PDT) has been investigated for use in a wide variety of tumors, including esophageal cancer, cholangiocarcinoma, prostate, bladder, lung, breast, brain (where it is administered intraoperatively), skin, and head and neck cancers. Barrett’s esophagus has also been treated with PDT.

**Obstructing Tumors**

Esophageal cancer is usually diagnosed at an advanced stage. A common clinical manifestation is dysphagia caused by obstruction of the esophagus by the tumor. There are several nonsurgical approaches to provide palliation of dysphagia including PDT.

Lung cancer is a common cause of airway obstruction that can manifest as dyspnea, coughing, and wheezing. The intervention used to manage obstruction depends on several factors, including etiology and acuteness. For patients without life-threatening airway obstruction, PDT is an option for providing palliative relief of symptoms.

**Early-Stage Lung Cancer**

Less than one-third of lung cancer patients present with early-stage disease. For patients with early-stage disease, surgery is the standard treatment. For inoperable early non-small-cell lung cancer, treatment guidelines from the National Comprehensive Cancer Network recommend stereotactic ablative radiotherapy. The guidelines reference a 2009 phase 2 multicenter noncomparative trial of
stereotactic body radiotherapy assessing 57 patients with inoperable stage I non-small-cell lung cancer, the results of which demonstrated a 3-year overall survival of 88%.² For patients who are not surgical candidates or who refuse surgery and are ineligible for radiotherapy, other ablative techniques (eg, PDT) are options.

Barrett Esophagus
The esophagus is normally lined by squamous epithelium. Barrett esophagus is a condition in which 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. Barrett esophagus occurs in the distal esophagus; it may involve any length of esophagus, it may be focal or circumferential, and it is visualized on endoscopy with a different color than background squamous mucosa. Confirmation of Barrett esophagus requires biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and patients with Barrett esophagus are at a 40-fold increased risk for developing this disease compared with the general population. Esophageal adenocarcinoma is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, resulting in histologic phenotypic expression ranging from low-grade dysplasia to high-grade dysplasia (HGD) to carcinoma. Most patients with nondysplastic Barrett esophagus do not progress beyond nondysplasia; the estimated rate of progression is 0.9% per patient per year.³ By comparison, the rate of progression from low-grade dysplasia to either HGD or esophageal adenocarcinoma ranges from 0.5% to 13.4% per patient per year.⁴ Once HGD is present, the risk of developing adenocarcinoma is 2% to 10% per patient per year; approximately 40% of patients with HGD on biopsy are found to have associated carcinoma in the resection specimen.³

Cholangiocarcinoma
Cholangiocarcinoma is rare and prognosis is generally poor due to advanced stage at presentation. Patients with unresectable cholangiocarcinoma typically decline rapidly with symptoms of biliary obstruction. Several palliative therapies have been suggested, including PDT, to reduce symptoms and improve quality of life.

Photodynamic Therapy
Several photosensitizing agents have been used in PDT: porfimer sodium (Photofrin), administered intravenously 48 hours before light exposure, and 5-aminolevulinic acid (5-ALA), administered orally 4 to 6 hours before the procedure. Aminolevulinic acid is metabolized to protoporphyrin IX, which is preferentially taken up by the mucosa. Clearance of porfimer occurs in a variety of normal tissues over 40 to 72 hours, but tumor cells retain porfimer for a longer period. Laser treatment of Barrett esophagus may be enhanced by the use of balloons containing a cylindrical diffusing fiber. The balloon compresses the mucosal folds of the esophagus, thus increasing the likelihood that the entire Barrett mucosa is exposed to light. All patients who receive porfimer become photosensitive and must avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days.
**Regulatory Status**
Labeled indications for porfimer sodium (Photofrin®; Pinnacle Biologics, Bannockburn, IL), as approved by the U.S. Food and Drug Administration (FDA) through a new drug application in 2011, are as follows.\(^5\)

**Esophageal Cancer**
- Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

**Endobronchial Cancer**
- Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small-cell lung cancer.
- Treatment of microinvasive endobronchial non-small-cell lung cancer in patients for whom surgery and radiotherapy are not indicated.

**High-Grade Dysplasia in Barrett Esophagus**
- Treatment of high-grade dysplasia in Barrett esophagus patients who do not undergo esophagectomy.

As of June 2017, oral 5-ALA has not received FDA approval as a photosensitizing agent for PDT. Topical 5-ALA, used for treatment of actinic keratoses, is addressed separately.

This evidence review addresses only the nondermatologic oncology applications of PDT and does not address its use in dermatologic applications, such as actinic keratosis and superficial basal cell cancer, or age-related macular degeneration. In addition, PDT should not be confused with extracorporeal photopheresis, which involves withdrawing blood from the patient, irradiating it with ultraviolet light, and then returning the blood to the patient. Extracorporeal photopheresis is addressed separately.

**Rationale**
This evidence review was created in December 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through June 02, 2017. Most studies from outside the United States use photosensitizing agents that have not been cleared for use in the United States.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes compared with available alternatives. The optimal study design for this purpose is a randomized controlled trial (RCT) that compares the therapeutic intervention with existing alternative treatments and 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.

**Photodynamic Therapy**

In 2010, the U.K.’s National Institute for Health Research published a systematic review of photodynamic therapy (PDT) for the treatment of precancerous skin conditions, Barrett esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus, and skin.³ Reviewers included literature published through June 2009 and included 88 trials. They noted a number of limitations in the body of evidence including few well-conducted, adequately powered RCTs, methodologic limitations, and gaps in evidence, rendering conclusions uncertain. Reviewers’ conclusions are summarized as follows: For Barrett esophagus, PDT in addition to omeprazole appeared to be more effective than omeprazole alone at long-term ablation of high-grade dysplasia (HGD) and slowing/preventing progression to cancer. No firm conclusions could be drawn for esophageal cancer. Further research into the role of PDT in lung cancer was recommended. For cholangiocarcinoma, reviewers concluded that PDT might improve survival compared with stenting alone. There was limited evidence on PDT for brain cancer and cancers of the head and neck. A wide variety of photosensitizers were used and, overall, no serious adverse effects were linked to PDT.

**Obstructing Esophageal Tumors**

When PDT is used for palliative treatment, relevant outcomes include short-term resolution of symptoms, such as dysphagia (difficulty swallowing). Long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting. The prescribing information for porfimer sodium (Photofrin) describes a 2010 multicenter, single-arm study of PDT in 17 patients with obstructing esophageal cancer.⁶ Patients received from 1 to 3 monthly treatments. Of 17 treated patients, 11 (65%) received clinically important benefit from PDT (defined as complete tumor response, normal swallowing, or improvement in dysphagia). After PDT, endoscopic débridement of the esophagus may be required, and residual tumor can be retreated during this process.

A 2014 Cochrane review² of treatments for dysphagia in esophageal cancer identified 2 1995 RCTs⁸,⁹ that compared laser treatment with PDT (total N=278 patients) and an RCT of argon plasma coagulation (APC) alone, APC with PDT, or APC with high-dose rate (HDR) brachytherapy (Rupinski et al, 2011,¹⁰ discussed below). Results for laser vs PDT were driven by the larger trial (N=236). The risk of bias for the smaller RCT was rated as unclear while the risk of bias for the larger RCT was rated as low. In meta-analysis, there was no statistical difference between treatments for improvement in dysphagia. The incidence of fever and photosensitivity were lower with laser treatment, and the incidence of perforation was lower with PDT. However, these estimates were imprecise because of very wide confidence intervals (CIs).
McCann et al (2011) reported on a systematic review of traditional nonendoscopic and endoscopic treatments for early esophageal cancer, including 26 PDT studies. Reviewers noted the lack of evidence from large, randomized trials and found the overall quality of evidence low. Although evidence demonstrated reduced morbidity and mortality with endoscopic techniques compared with esophagectomy, outcomes across endoscopic treatments were similar, and no single endoscopic technique was identified as a recommended treatment approach. Reviewers focused on tumor response and recurrence and disease-specific and overall survival (OS) and did not examine quality of life outcomes.

In 2011, Rupinski et al, which was also included in the 2014 Cochrane review summarized above, reported on a randomized trial of 93 patients with inoperable cancer of the esophagus or esophageal junction who were treated with APC alone, APC with PDT, or APC with HDR brachytherapy. Both combination therapies were more effective than APC alone when it came to median time to recurrence of dysphagia (85, 59, and 35 days for APC with HDR, APC with PDT, and APC alone, respectively). OS did not differ significantly between groups. However, complications occurred more often in the APC with PDT and APC alone groups than in the APC with HDR group.

**Section Summary: Obstructing Esophageal Tumors**

At least 3 RCTs have compared various treatments including Nd:YAG laser or PDT plus APC with HDR brachytherapy plus APC or APC alone for dysphagia in esophageal cancer. Meta-analysis comparing PDT with Nd:YAG laser has suggested that improvements in dysphagia are similar, although estimates are imprecise. PDT is associated with a lower risk of perforation compared with laser; however, PDT runs a high risk of patients reacting adversely to light (eg, photosensitivity). PDT plus APC appears to prolong time to recurrence of dysphagia compared with APC alone.

**Obstructing Endobronchial Tumors**

For obstructing esophageal tumors, short-term outcomes are relevant. Because laser ablation is commonly used to treat endobronchial lesions, the comparative efficacy of PDT and laser ablation is relevant. The Photofrin prescribing information cites 2 studies with 211 patients with obstructing endobronchial tumors who were randomized to PDT or Nd:YAG (neodymium-doped yttrium aluminum garnet) laser therapy. Response rates (ie, the sum of complete response and partial response rates) for the 2 treatments were similar at 1 week (59% PDT, 58% laser therapy), with a slight improvement at 6 weeks for PDT (60% PDT, 41% laser therapy). Clinical improvement, defined as improvements in dyspnea, cough, and hemoptysis, were similar for both groups at 1 week (25%-29%); however, at 1 month and beyond, 40% of patients treated with PDT reported clinical improvement compared with 27% treated with laser therapy. Statistical comparisons were not performed due to missing data.

A 2014 RCT comparing neoadjuvant chemotherapy with or without PDT in 42 patients with inoperable, locally advanced, obstructing non-small-cell lung cancer (NSCLC) showed a greater proportion of patients who received PDT were able to
undergo complete resection (pulmonectomy or lobectomy) compared with patients who did not receive PDT (89% vs 54%; p=0.002 [author calculation]).

Diaz-Jimenez et al (1999), in a small, randomized study, compared PDT with Nd:YAG laser therapy in 31 patients who had airway obstruction. Efficacy over 24 months was similar. The incidence of immediate response was greater with laser therapy than with PDT, suggesting that laser therapy may be particularly appropriate for patients requiring rapid symptom relief.

Section Summary: Obstructing Endobronchial Tumors
At least 3 RCTs have compared PDT with laser for symptom improvement in patients with obstructing endobronchial tumors. Patients have generally reported similar improvements in symptoms with PDT and with laser. One additional RCT noted that adding PDT to neoadjuvant chemotherapy may increase the probability of undergoing complete surgical resection.

Early-Stage Lung Cancer
It is anticipated that relatively few patients with nonobstructing lung cancer (who are not candidates for surgery) will be appropriate candidates for PDT. Of the 178,000 new cases of lung cancer annually, only 15% are detected with early-stage lung cancer. Of these, approximately 60% are treated with surgery, and another 25% are treated with radiotherapy. Candidates for PDT are limited to those patients who cannot tolerate surgery or radiotherapy, most commonly due to underlying emphysema, other respiratory disease, or prior radiotherapy. In this primary treatment setting, long-term outcomes such as response rates and disease-free survival are important. The prescribing information for porfimer sodium (Photofrin) describes 3 case series of 62 patients with microinvasive lung cancer. Complete tumor response rate, biopsy-proved, at least 3 months after treatment was 50%; the median time to tumor recurrence exceeded 2.7 years; the median survival was 2.9 years; and disease-specific survival was 4.1 years. In another case series (1996) of 95 early-stage lung cancers treated with endoscopic PDT, the complete response rate was 83.2%. A summary of case series describing the use of porfimer sodium PDT for early-stage lung cancer is shown in Table 1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>N</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furukawa et al (2005)</td>
<td>Early-stage, central-type lung cancers</td>
<td>93</td>
<td>Lesion &lt;1 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CR: 93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 5-y survival: 58%</td>
</tr>
<tr>
<td>Corti et al (2007)</td>
<td>Early inoperable or recurrent NSCLC</td>
<td>40</td>
<td>CR: 72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR: 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR: 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median survival: 91 mo</td>
</tr>
<tr>
<td>Moghissi et al</td>
<td>Early central lung cancer,</td>
<td>21</td>
<td>CR: 100%</td>
</tr>
</tbody>
</table>
The labeled indication for porfimer sodium suggests that PDT for early-stage lung cancer should be limited to those who are not candidates for surgery or radiotherapy. However, Cortese et al (1997) reported on a case series of 21 patients with early-stage squamous cell lung cancer who were offered PDT as an alternative to surgery. Patients were followed closely and underwent repeat endoscopy and/or surgical resection if cancer persisted after 1 or 2 courses of PDT. Nine (43%) patients had a complete response at a mean follow-up of 68 months (range, 24-116 months) and thus were spared surgical treatment.

It should be noted that Nd:YAG laser therapy, electrocautery, cryotherapy and endobronchial brachytherapy also are considered treatment options for early-stage lung cancer in patients who are not candidates for surgery or radiotherapy. However, only case series are available supporting their use and no controlled studies have compared the safety and efficacy of these techniques in treatment of early-stage disease.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>N</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2007)(^17)</td>
<td>ineligible for surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo et al (2009)(^18)</td>
<td>Centrally located early lung cancer; longitudinal tumor length ≤10 mm</td>
<td>48</td>
<td>CR: 94% 5-y survival: 81%</td>
</tr>
<tr>
<td>FDA (Photofrin prescribing information) (2011)(^5)</td>
<td>Microinvasive, inoperable endobronchial tumors</td>
<td>62</td>
<td>CR at 3 mo: 50% Median survival: 2.9 y (2.1 to 5.7)</td>
</tr>
</tbody>
</table>


### Section Summary: Early-Stage Lung Cancer

The evidence for PDT as a treatment for early-stage lung cancer in patients for which surgery and radiotherapy are not options consists of several case series, including between 21 and 95 patients. Complete response rates ranged from 72% to 100%. Survival outcomes were not consistently reported and varied; 5-year survival rates ranged from 58% to 81% when reported and the median survival ranged from 3 years to over 7 years when reported. No comparative studies are available; however, survival rates seem consistent with case series available for other methods such as radiofrequency ablation, cryotherapy, or brachytherapy. Given the low number of early-stage lung cancer patients who are not candidates for surgery or radiotherapy, it is unlikely that stronger evidence will become available.

### Barrett Esophagus With HGD

A 2012 review of endotherapy for Barrett esophagus indicated that, although studies have demonstrated long-term success with PDT for the treatment of HGD in Barrett esophagus, its disadvantages have limited its continued use compared with newer modalities. Cited limitations of PDT included photosensitization, stricture formation, buried glands that harbor neoplastic potential, and decreased efficacy compared with new technologies.
Randomized Controlled Trials
The U.S. Food and Drug Administration (FDA)‒approved indication for treatment of HGD was based on a multicenter, partially blinded, study that randomized 199 patients to porfimer sodium (Photofrin) plus omeprazole or to omeprazole alone. Initially, 485 patients with HGD were screened for the trial; 49% were subsequently excluded because HGD was not confirmed on further evaluation. As noted in the prescribing information, the high patient exclusion rate reinforces the recommendation by the American College of Gastroenterology that the diagnosis of dysplasia in Barrett esophagus be confirmed by an expert gastrointestinal pathologist. Patients randomized to the treatment group received up to 3 courses of PDT separated by 90 days. The primary efficacy end point was the complete response rate at any one of the endoscopic assessment time points. Complete response was defined as ablation of all areas of HGD but some areas of low-grade dysplasia or Barrett epithelium may remain. Complete response was achieved by 76.8% of patients in the treatment group and 38.6% in the control group. After 24 months of follow-up, 13% of patients in the treatment group and 28% of patients in the control group had progressed to cancer.

Five-year follow-up of patients in the RCT previously described was reported by Overholt et al (2007). Sixty-one patients with Barrett esophagus and HGD were enrolled in the long-term phase of the trial; 48 were randomized to PDT plus omeprazole group, and 13 were randomized to omeprazole only. Endoscopy with mucosal assessment and biopsy was performed at the first visit and every 3 months thereafter until 4 consecutive quarterly biopsy results were negative for HGD and then biannually until 60 months after randomization or until treatment failure. At 5 years, PDT plus omeprazole (77% [106/138]) was significantly more effective than omeprazole alone (39% [27/70]; p<0.001) in eliminating HGD. Patients in the PDT group (15% [21/138]) were approximately half as likely to progress to cancer as those in the omeprazole alone group (29% [20/70]; p=0.027), with a significantly longer time to progression with PDT. Serious complications were reported by 12% of PDT patients vs 1% omeprazole patients. Thirty-six percent of PDT patients developed strictures. The study was limited by the small number of patients available for long-term follow-up.

In 2013, Dunn et al reported on an RCT that compared 5-aminolevulinic acid (5-ALA)‒mediated PDT - with porfimer-mediated PDT for the treatment of 64 patients with Barrett esophagus with HGD. (Note: Oral ALA does not have FDA approval as a photosensitizing agent for PDT.) Patients were recruited from a single university hospital in England. At 1 year, complete reversal of dysplasia occurred in 16 (47%) of 34 patients randomized to 5-ALA and in 12 (40%) of 30 patients randomized to porfimer (p=0.62). With median follow-up of 2 years, 3 prevalent cancers occurred in each group within 12 months of treatment; and 3 incident cancers occurred more than 12 months after treatment, one in the 5-ALA group and two in the porfimer group. Overall cancer incidence was 12% and 17% in the 5-ALA and porfimer groups, respectively (p=0.240). Strictures (26% vs 7%) and photosensitivity (43% vs 6%) were more common with porfimer. Pleural effusions (7% vs 18%) and transaminitis (0% vs 47%) were more common with 5-ALA.
Observational Studies
Badreddine et al (2010) retrospectively analyzed a cohort of Barrett esophagus patients seen at a specialized clinic in the United States to identify risk factors for recurrence of dysplasia after ablative treatment including PDT. Three hundred sixty-three patients underwent PDT with or without endoscopic mucosal resection. Forty patients were lost to follow-up, 46 had residual dysplasia, and 12 had no dysplasia at baseline. Indications for ablation were low-grade dysplasia in 53 patients, HGD in 152 patients, and intramucosal cancer in 56 patients. Median follow-up was 36 months. Recurrence occurred in 45 patients, and median time to recurrence was 17 months. Significant predictors of recurrence in the multivariate model were older age, presence of residual nondysplastic Barrett epithelium, and a positive smoking history. Authors noted that missing prevalent dysplasia (despite aggressive surveillance) might have limited study conclusions.

Pech et al (2008), in a study from Germany, reported 5-year outcomes of endoscopic treatment of high-grade intraepithelial neoplasia and mucosal adenocarcinoma in patients with Barrett esophagus. Patients were excluded if staging examinations did not confirm the suspected diagnosis of Barrett metaplasia or high-grade intraepithelial neoplasia, or if more advanced tumor stage (>T1), lymph-node involvement, or metastasis was present. Patients with localized neoplasia were offered endoscopic resection; those with lesions not clearly localized, those with superficial subtle multifocal neoplasia, and patients with no neoplasia on esophageal biopsy received PDT with 5-ALA. Fifty-five patients received only PDT, and 13 underwent endoscopic resection and PDT. Complete response was achieved in 98.5% of patients; during median follow-up of 37 months, 17% of patients experienced cancer recurrence.

Prasad et al (2007) reported on similar outcomes for 2 nonrandomized groups of patients who received PDT (n=129) or surgery (n=70) for HGD in Barrett esophagus. Mortality rates were 9% and 8.5% in the PDT and surgery groups, respectively, over a median follow-up of 59 months for the PDT group and 61 months for the surgery group.

Section Summary: Barrett Esophagus With HGD
One RCT comparing PDT plus a proton pump inhibitor with a proton pump inhibitor alone demonstrated that a higher response rate and a lower risk of progression to cancer persisted during the 5-year follow-up for PDT; however, long-term follow-up is only available for a small number of patients. In addition, PDT patients had significantly more complications, including a high rate of strictures. Observational comparative data have suggested similar mortality outcomes for PDT and esophagectomy over 5 years.

Cholangiocarcinoma
There is ongoing interest in PDT as an adjunct to endoscopic management of cholangiocarcinoma, primarily as a palliative strategy. In addition, percutaneous biliary drainage is a frequent management strategy for cholangiocarcinoma, and PDT can thus be administered percutaneously.
Systematic Reviews
A 2012 review of PDT for unresectable cholangiocarcinoma concluded that, although data and experience with PDT are limited, PDT can be considered a standard palliative therapy for unresectable cholangiocarcinoma.²⁶

Gao et al (2010) performed a systematic review of the literature on PDT for unresectable cholangiocarcinoma²⁷; Two RCTs, 2 comparative trials with concurrent controls, 1 comparative trial with historical controls, and 15 case series were included. The 2 randomized trials were rated moderate quality, and the other studies were low-to-moderate quality. Mean number of subjects was 27 (range, 1-184 subjects). Porfimer sodium (Photofrin) was the photosensitizing agent used in all but two of the included studies. The most commonly reported adverse events were cholangitis (28%), phototoxicity (10%), and biloma (2%).

Lu et al (2015) reported on a meta-analysis of controlled trials of PDT for unresectable cholangiocarcinoma published through December 2013.²⁸ Eight controlled trials (total N=642 patients) were included; the two RCTs were the same RCTs identified in Gao (2010). In the 7 trials (n=602 patients) of PDT plus stent vs stent-alone, OS was significantly longer in PDT plus stent (hazard ratio, 0.49; 95% CI, 0.33 to 0.73; p<0.01). Two studies reported that Karnofsky Performance Status scores were higher in patients receiving PDT but quantitative summaries were not given. Cholangitis was reported in 36% of patients who received PDT and 34% of patients who did not. Eleven percent of patient receiving PDT had a phototoxic reaction.

Randomized Controlled Trials
The two small randomized studies described in the Gao (2010) systematic review reported both palliative effects and an increase in median survival. Ortner et al (2003) conducted a trial of 39 patients with nonresectable cholangiocarcinoma who were randomized to endoscopic stenting alone or in conjunction with PDT.²⁹ Median survival of the 20 patients in the PDT group was 493 days compared with 98 days in the 19 patients who underwent stenting alone. The trial was terminated prematurely due to these favorable results. Zoepf et al (2005) randomized 32 patients with cholangiocarcinoma to stenting with and without temoporfin (Foscan) PDT.³⁰ Median survival was 21 months for the PDT group compared with 7 months in the control group.

Hauge et al (2016) reported results of a phase 2 safety and feasibility RCT for combination chemotherapy plus stenting with and without temoporfin (Foscan) PDT in the treatment of biliary tract cancer.³¹ Eligible patients had unresectable or recurrent/metastatic biliary tract cancer, no previous chemotherapy or radiotherapy for the current cancer, and no other cancers in the previous 5 years. Twenty patients were enrolled; 17 had hilar cholangiocarcinoma. In the PDT group, one PDT treatment was given following stenting and before chemotherapy. Chemotherapy was given until progression or for 12 courses. No serious, procedure-related adverse events were observed in either group. The number of grade 3 and 4 adverse events was similar in both groups. Three patients in each group developed cholangitis within 30 days. Following chemotherapy, mean quality
of life as measured by the EORTC QLQ-C30 symptom score (range, 0-100) was 33 vs 24 for the fatigue domain, 14 vs 19 for the nausea and vomiting domain, and 14 vs 10 for the pain domain for PDT vs no PDT, respectively. Precision estimates were not given. Median progression-free survival was 139 days (range, 26-600 days) vs 96 days (range, 56-422 days) in PDT vs no PDT, respectively. Median OS was 238 days (range, 178-1060) in the PDT group and 336 days (range, 110-690 days) in the no-PDT group.

**Observational Studies**

Pereira et al (2012) reported on a prospective cohort study of 34 patients with unresectable cholangiocarcinoma who were treated with porfimer-mediated PDT at 3 centers in England. Median survival was approximately 13 months with or without chemotherapy. At 5-year follow-up, all but 1 patient had died (5-year OS=3%), most due to disease progression.

Kahaleh et al (2008) retrospectively evaluated 19 patients treated with endoscopic retrograde cholangiopancreatography (ERCP) with PDT and stents, and 29 patients treated with ERCP and stents alone at a U.S. center. All patients had unresectable cholangiocarcinoma; most had Bismuth type III and IV lesions (involvement of left and/or right secondary hepatic ducts). Some patients in each group received chemoradiotherapy. Mortality rates at 3, 6, and 12 months were 0%, 16%, and 56%, respectively, in the PDT plus stent group, and 28%, 52%, and 82%, respectively, in the stent-alone group. Differences were statistically significant at 3 and 6 months. The authors noted that “it remains to be proved whether this effect is attributable to PDT or the number of ERCP sessions, and a randomized multicenter study is required to confirm these data.”

In a comparative review with concurrent controls, Witzigmann et al (2006) analyzed records of 184 patients treated over a 10-year period in Germany for hilar cholangiocarcinoma. Sixty patients underwent resection (8 after neoadjuvant PDT), 68 had PDT plus stenting, and 56 had stenting alone. Median survival was 12 months in the PDT plus stenting group vs 6.4 months in the stent-alone group (p<0.01). Patients who received PDT plus stenting had lower serum bilirubin levels (p<0.05) and higher Karnofsky Performance Status scores (p<0.01).

Several case series have reported positive quality of life outcomes with PDT. In a 2008 editorial, Baron reviewed the pros and cons of PDT for palliation of cholangiocarcinoma and the questions remaining about its role given the available options of chemoradiation, brachytherapy, and plastic and metal stents. On the negative side, he noted that PDT is not available at all centers and requires expertise in both endoscopy and PDT; laser fibers available in the United States are suboptimal for ERCP use—because of their stiffness, treatment is limited to the main hepatic ducts; the procedure is time-consuming; and posttreatment photosensitivity lasts for 4 to 6 weeks, potentially limiting quality of life. In favor of PDT, the procedure is reasonably well-tolerated, seems to be effective, can be repeated without a ceiling dosage effect, and is the only treatment to date for which data suggest improved survival over plastic stent placement alone for
advanced cholangiocarcinoma. Baron concluded that the answer to whether PDT should be used for palliation of cholangiocarcinoma is a “qualified yes” but that “further comparative trials are needed to determine the optimal regimen of palliation of obstructive jaundice in these patients.”

**Section Summary: Cholangiocarcinoma**

Several observational studies as well as 2 small RCTs have found that PDT plus stenting is associated with greater elimination of bile duct stenosis and improved survival benefit. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival but not OS with similar rates of adverse events. Case series have suggested an improvement in quality of life. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small number of cholangiocarcinoma patients, it is unlikely that stronger evidence will become available.

**Other Malignancies**

**Gynecologic Malignancies**

Godoy et al (2013) reported on a retrospective cohort of women with recurrent gynecologic malignancies who were treated with porfimer-mediated PDT at a single U.S. center; 32 patients with recurrent gynecologic malignancies (9 cervical, 6 vulvar, 6 vaginal, 5 ovarian, 5 endometrial, 1 recurrent Paget disease of the anal canal) were treated with porfimer-mediated PDT. Three (24%) of 21 patients who had vaginal, cervical, or anal recurrences achieved complete response (defined as a lack of detectable lesions within the area of treatment). Median time to response was 28 months. Some patients received more than 1 treatment. Patients with vaginal and cervical recurrences also had moderate-to-severe burning sensation, with maximum treatment for 3 weeks.

**Endometrial Cancer**

In a retrospective Korean cohort study, Choi et al (2013) investigated the use of PDT as a fertility-sparing treatment for patients with early-stage (confined to the endometrium) endometrial cancer. Sixteen patients were treated with PDT for grade 1 or 2 disease at an age younger than 35 years (mean, 31 years; range, 24-35 years). The photosensitizing agent was Photogem (non-FDA-approved) administered intravenously. Mean follow-up from diagnosis was 78 months (range, 8-140 months). After initial PDT, 12 (75%) of 16 patients showed complete response (defined as complete disappearance of adenocarcinoma or hyperplasia on follow-up dilation and curettage, and 4 patients were nonresponders. Four (33%) of the 12 initial responders recurred 6 months after complete response; 2 responded after additional PDT treatments. One of 4 initial nonresponders achieved complete response after a second PDT treatment. Seven patients attempted to become pregnant, all initial responders. Four (57%) patients had 7 pregnancies, four with artificial reproducte technology and three by natural means, resulting in 6 live births. All were by cesarean delivery. No evidence of endometrial cancer recurrence or hyperplasia was found before or after childbirth.

In a similar study, Choi et al (2014) retrospectively reviewed 21 patients, ages 45 years or younger at diagnosis of early-stage (90% IA1 or IB1) cervical cancer who
underwent a loop electrosurgical excision procedure or conization followed by PDT.\textsuperscript{41} This treatment was considered a fertility-preserving alternative to vaginal radical trachelectomy (excision of the uterine cervix). Median patient age was 31 years. At mean follow-up of 53 months, 1 (5\%) patient relapsed. Ten (77\%) of 13 patients who attempted pregnancy were successful; live birth occurred in 7 cases, five of which were full-term deliveries.

**Cervical Intraepithelial Neoplasia**

In 2014, Tao et al in China published a systematic review of PDT for cervical intraepithelial neoplasia (CIN).\textsuperscript{42} Literature was searched through March 2012, and 14 studies, mostly cohort studies and case series, were included (total N=472 patients). Criteria for PDT efficacy varied across studies, but most (10/14) required biopsy. Overall, complete response rate ranged from 0\% to 100\%. Two small RCTs (total n=60 patients) and 1 small case-control study (N=22) found no difference in complete response rate between PDT and placebo, PDT with hexylaminolevulinate (HAL) and PDT with methylaminolevulinate, or PDT and conization. Seven studies (n=319 patients) reported human papillomavirus (HPV) eradication rates ranging from 53\% to 80\%.

In 2015, Hillemanns et al reported on an international RCT of PDT with HAL in patients with CIN grades 1 or 2.\textsuperscript{43} Patients with CIN grade 1 or 2 by local pathology review were randomized to 5\% HAL, 1\% HAL, 0.2\% HAL, or placebo. Ointment and illumination (in active treatment groups) were applied by an indwelling device for 5 hours and 4.6 hours, respectively. The primary efficacy end point was patient response at 3 months, defined by regression of CIN and clearance of oncogenic HPV. After blinded central pathology review, 79\% of randomized patients were confirmed as having CIN grade 1 or 2 and were included in efficacy analyses. Of these patients, 49\% with CIN grade 1 and 83\% with CIN grade 2 had oncogenic HPV infection. Statistically significant differences in complete response at 3 months compared with placebo were observed only for patients with CIN grade 2 who received 5\% HAL (18 [95\%] of 19 patients vs 12 [57\%] of 21 patients; p=0.009). All responders in both groups maintained response 6 months after last treatment. Five (2\%) of 262 randomized women became pregnant within 3 months of last treatment, and all delivered healthy full-term infants. Interpretation of these results was limited by the lack of randomization among patients included in efficacy analyses and lack of statistical correction for multiple testing.

In a study included in the Tao systematic review, Istomin et al (2010) reported on 112 patients with morphologically proven CIN grades 2 and 3 with at least 1 year of follow-up after treatment with Photolon (a non-FDA-approved photosensitizing agent) PDT.\textsuperscript{44} Complete regression of neoplastic lesions was seen in 104 (93\%) of treated women. Of 88 patients infected with highly oncogenic strains of HPV, 47 (53\%) had complete eradication of HPV infection 3 months after treatment. Fifteen women became pregnant after treatment and recovery; live births occurred in 8 cases, six by “normal delivery” and two by cesarean delivery.
Subsequent to the literature search of the Tao review, Soergel et al (2012) reported on 72 patients with histologically confirmed CIN grade 1, 2, or 3 who were treated with PDT at a single center in Germany. Patients were randomized to 1 of 6 treatment groups defined by varying dosages of the photosensitizing agent, HAL or methylaminolevulinate (neither FDA-approved for systemic use). The primary end point was complete response at 6 months, defined as normal histology and cytology. Women treated with HAL 40 mM applied twice in 3 hours (vs 12 hours) followed by a light dose of 50 to 100 J/cm$^3$ had the best response (83% among women with CIN grade 2). Groups were not powered for statistical comparison.

**Vulvar Intraepithelial Neoplasia**

Winters et al (2008) reported on a phase 2 European study of imiquimod and PDT for vulvar intraepithelial neoplasia in 20 patients. At baseline, 95% of patients were symptomatic; at 52 weeks, 65% of patients were asymptomatic. A potential benefit of PDT is treatment of multifocal disease. Results from this small trial require replication in larger studies.

**Section Summary: Gynecologic Malignancies**

The evidence for PDT in gynecologic malignancies includes mostly uncontrolled observational studies; 2 RCTs have been conducted in cervical cancer. The evidence for the efficacy is mixed with complete response for PDT in cervical cancer ranging from 0% to 100% and HPV eradication rates ranging from 53% to 80%. Only a small number of patients with other gynecologic malignancies treated with PDT have been studied.

**Bladder Cancer**

Investigators in Germany and Korea have examined cohorts with non-muscle-invasive bladder cancer treated with PDT after transurethral resection of the bladder. Bader et al (2013) applied intravesical hexaminolevulinate (Hexvix) and bladder wall irradiation to 17 patients with intermediate- or high-risk urothelial cell carcinoma. Six-, 9-, and 21-month disease-free survival rates were 53%, 24%, and 12%, respectively. Lee et al (2013) applied intravenous Radachlorin (non-FDA-approved) and bladder wall irradiation to 34 patients with high-grade urothelial cell carcinoma refractory or intolerant to bacillus Calmette-Guérin therapy (for recurrence prevention). Recurrence-free survival rates at 12, 24, and 30 months were 91%, 64%, and 60%, respectively.

**Head and Neck Cancers**

**Systematic Reviews**

Gondivkar et al (2017) published a systematic review of PDT for the management of potentially malignant oral disorders and head and neck squamous cell carcinoma. Twenty-six studies (total N=988 patients; range, 2-147 patients) of several different photosensitizers were included (ALA, meta-tetrahydroxyphenylchlorin, Foscan, hematoporphyrin derivatives, Photofrin, Photosan, and chlorin e6). Reviewers stated that the studies were all prospective; only 1 study was comparative. In the studies reporting response rates, complete,
partial, and no response rates to PDT ranged from 23% to 100%, 4% to 66%, and 0% to 39%, respectively, for potentially oral malignant disorders, and complete response rates ranged from 16% to 100% for head and neck carcinoma. The recurrence rate for potentially malignant oral disorders ranged from 0% to 36% in 12 studies.

A 2013 systematic review from The Netherlands reported on m-tetrahydroxyphenylchlorin (mTHPC [Foscan]; non-FDA-approved)–mediated PDT of squamous cell carcinoma of the head and neck.50 Twelve studies met inclusion criteria. Six reported on PDT with curative intent and six as palliative treatment. Data from 4 studies reporting on curative therapy were pooled (n=301 patients). Reviewers concluded that data are insufficient to permit conclusions on PDT for curative intent and that randomized trials were needed. Palliative therapy appeared to increase quality of life by approximately 30% at 4 months for those with head and neck cancer, as measured by the University of Washington Quality of Life Questionnaire and the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer.

In 2009, Wildeman et al reviewed evidence on the efficacy of PDT in patients with recurrent nasopharyngeal carcinoma.51 Of 5 studies included, one was a series of 135 patients, which reported complete response in 76 (56%) cases and a marked response in 47 (35%) cases after hematoporphyrin derivative–mediated PDT; however, it was unclear whether PDT was first- or subsequent-line treatment. The other 4 studies had 12 or fewer subjects.

**Comparative Studies**

At a single center in The Netherlands, Karakullukcu et al (2013) conducted a retrospective, matched cohort study of 98 patients with primary T1/T2N0M0 squamous cell carcinoma of the oral cavity to a maximum depth of 5 mm.52 The study compared mTHPC-mediated PDT with surgery. Fifty-five patients received PDT, and a cohort of 43 patients matched by age, sex, presentation (primary or secondary), and tumor location, depth, and stage underwent transoral surgery. There was no statistical difference between groups in 5-year disease-free survival (47% vs 53% in the PDT and surgery groups, respectively; Cox proportional hazard, p=0.75), 5-year local recurrence-free survival (67% vs 74%; p=0.13), or OS (83% vs 75%; p=0.17).

**Noncomparative Studies**

Ahn et al (2016) reported outcomes of a phase 1 study of PTD with ALA for premalignant and early-stage head and neck tumors.53 Thirty-five patients were enrolled and 30 received PDT ranging from 50 to 200 J/cm². The median follow-up was 42 months. The most common toxicity was grade 3 mucositis (52%). One patient developed grade 5 sepsis and died, which might have been related to treatment. The complete response rate at 3 months was 69%. Including all follow-up, 34% of patients developed local recurrence and 34% developed recurrence adjacent to the treated field.
In 2007, Biel reported his own experience with 276 patients treated with PDT with Photofrin for early oral and laryngeal cancers over a period of nearly 16 years and summarized previously published small case series. Of 115 patients in this case series who had recurrent or primary carcinoma-in-situ, T1N0 and T2N0, the 5-year cure rate was 100%; at mean follow-up of 91 months, there were 10 recurrences. For 113 patients with recurrent or primary carcinoma-in-situ and T1N0 squamous cell carcinoma of the oral cavity, there were 6 recurrences within 8 months of initial treatment salvaged with either repeat PDT or surgical resection. Two patients with T1 tongue tumors developed positive regional lymph nodes within 3 months of PDT, had conventional neck dissection, and were disease-free for at least 5 years. In 48 patients treated for superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity, there were 5 recurrences, all salvaged with repeat PDT or surgical resection. The 3-year cure rate was 100% (mean follow-up, 56 months). These data require replication in larger, comparative trials.

Several small (sample size range, 7-30 patients), uncontrolled studies have been reported on PDT for laryngeal, oral, and nasopharyngeal cancers. Different outcomes were reported across studies. Of the studies reporting response rates, complete response was observed in 67% to 100% of patients treated with PDT. Two studies collected data on OS. One of these reported a 4-year OS rate of 67% and the other reported a 5-year OS rate of 36%.

**Section Summary: Head and Neck Cancers**

Evidence for use of PDT in head and neck cancers comprises primarily small cohort studies of mixed cancer types (laryngeal, oral, nasopharyngeal) and stage (early and advanced), line of treatment (primary and secondary), and intent (palliative and curative). Interpretation of results is limited by lack of comparator groups. One retrospective matched cohort study compared PDT with surgery and found no between-group difference in survival outcomes.

**Mesothelioma**

PDT for the treatment of mesothelioma has also been discussed in recent reviews; however, identified studies are phase 1 and animal studies. A 2004 study from Austria with 14 subjects involved intraoperative PDT under hyperbaric oxygenation. In 2013, this same group published a retrospective study of 41 patients with malignant pleural mesothelioma who were treated surgically, 17 (41%) of whom received intraoperative porfimer-mediated PDT. Intraoperative PDT had no statistically significant impact on survival.

**Brain Cancer**

At 2 university hospitals in Japan, Muragaki et al (2013) applied intraoperative PDT to 22 patients with newly diagnosed (n=21) or recurrent (n=1) primary malignant parenchymal brain tumors (≈50% glioblastoma). The photosensitizing agent was talaporfin sodium (Laserphyrin; non-FDA-approved). At 6 months, 2 patients had local progression (6-month progression-free survival, 91%); at 1 year, 1 patient had died (1-year OS=95.5%). Median progression-free survival...
was 20 months (95% CI, 10.3 to not estimated), and median OS was 27.9 months (95% CI, 24.8 to not estimated).

Aziz et al (2009) used intraoperative PDT with Photofrin in 14 patients with metastatic brain cancer (7 originating in the lung and 7 from a variety of sources). Of the patients with lung cancer metastases, one died of unrelated cause, and six were free of brain disease until death. Two of the remaining patients (one with metastatic bowel cancer, one with unknown primary) died of local brain recurrence. A 2010 review of the literature on PDT applications in brain tumors relied largely on unpublished data and was not reviewed herein.

**Soft Tissue Sarcoma**
A 2013 retrospective, single-center study from Japan examined PDT in high-grade soft tissue sarcoma. Acridine orange, a non-FDA-approved fluorescent dye, was used as the photosensitizer in 51 PDT-treated patients. Compared with 119 patients who underwent conventional wide-margin resection for limb salvage surgery, there was no statistical difference in 10-year OS (p=0.75) or 10-year local recurrence (p=0.36).

**Other Applications**
PDT has been used for the treatment of pancreatic cancer, obstructive jaundice due to hepatocellular carcinoma, and oral premalignant lesions. There is little evidence of PDT’s efficacy for these indications.

**Summary of Evidence**
For individuals who have obstructing esophageal cancer who receive PDT as palliation, the evidence includes systematic reviews, RCTs, and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. A meta-analysis comparing PDT with Nd:YAG laser suggested that improvements in dysphagia are similar, although estimates are imprecise. PDT is associated with a lower risk of perforation compared with Nd:YAG laser treatment; however, PDT runs a higher risk that a patient might react adversely to the light (eg, photosensitivity). PDT plus argon plasma coagulation appears to prolong the time to recurrence of dysphagia as opposed to argon plasma coagulation alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have obstructing endobronchial cancer who receive PDT as palliation, the evidence includes RCTs and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Evidence from RCTs comparing PDT with Nd:YAG laser has generally supported improvements in symptoms with PDT similar to those with laser. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy who receive PDT, the evidence includes
uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. There are few patients with early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy; additionally, several treatment methods are available for this population. Studies comparing these treatment methods are not available. Case series of PDT include between 21 and 95 patients and have reported complete response rates ranging from 72% to 100%. Given the small size of this potential population and the ineligibility for standard surgical treatment or radiotherapy, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have Barrett esophagus with high-grade dysplasia who receive PDT, the evidence includes an RCT and observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The RCT compared PDT plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression to cancer persisting during 5 years of follow-up for PDT. The results of the RCT revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Observational comparative data suggested similar mortality outcomes for PDT and esophagectomy over 5 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable cholangiocarcinoma who receive PDT plus stenting as palliation, the evidence includes systematic reviews, RCTs, and observational studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Two small RCTs and several observational studies have found that PDT plus stenting is associated with greater elimination of bile duct stenosis and improved survival benefit than stenting alone. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival, but not overall survival, with similar rates of adverse events. Case series have suggested an improvement in quality of life with PDT. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small size of this potential population, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other malignancies (eg, gynecologic, bladder, head and neck, brain, soft tissue) who receive PDT, the evidence includes controlled observational studies and uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The published literature on PDT for these malignancies is generally comprised small case series without comparator groups. The evidence is insufficient to determine the effects of the technology on health outcomes.
Supplemental Information

Practice Guidelines and Position Statements

American College of Chest Physicians
In 2013, the American College of Chest Physicians updated its evidence-based guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways. The College recommended photodynamic therapy (PDT) and other endobronchial treatments (brachytherapy, cryotherapy, electrocautery) “for patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection” (grade 1C: strong recommendation based on low-quality evidence). The guidelines summarized the evidence for PDT in early lung cancer as follows:

“PDT appears to be an effective therapeutic modality for small early-stage centrally located lung cancers, the majority of which are squamous cell carcinomas. Complete response (CR) rates have been achieved in 32% to 100% of cancers, with the longitudinal length of the cancer being an important predictor of response. However, some patients experience local recurrences, and long-term outcomes remain suboptimal. Talaportin sodium (NPe6), a newer-generation photosensitizer, appears to be as effective but better tolerated than older agents. However, these data have only been reported by one group and need to be validated in larger numbers of patients.”

American Gastroenterological Association
The 2011 American Gastroenterological Association’s position statement on Barrett esophagus management recommended PDT as an option for treatment of confirmed high-grade dysplasia (HGD) with Barrett esophagus.

American College of Gastroenterology
The 2015 American College of Gastroenterology guidelines on diagnosis and management of Barrett esophagus stated that there is level I evidence for prevention of cancer for PDT and radiofrequency ablation in Barrett esophagus with HGD. The guidelines also stated: “Given the costs and side-effect profile of photodynamic therapy, as well as the large body of data supporting the safety and efficacy of radiofrequency ablation, this modality appears to be the preferred therapy for most patients.”

European Association of Urology
European Association of Urology updated its guidelines on non-muscle-invasive bladder cancer in 2017. PDT was not included as a treatment option.

National Comprehensive Cancer Network

Esophageal Cancer and Barrett Esophagus
National Comprehensive Cancer Network (NCCN) guidelines (v.1.2017) for esophageal cancer state that radiofrequency ablation has become the preferred
treatment while PDT is an alternative strategy for patients who have Barrett esophagus with HGD.74

The guidelines also state that PDT can effectively treat esophageal obstruction but “is less commonly performed due to photosensitivity and costs” compared with radiotherapy and brachytherapy.

**Cholangiocarcinoma**
NCCN guidelines (v.2.2017) describe PDT as a relatively new therapy for local treatment of unresectable cholangiocarcinoma, stating that the combination of PDT and biliary stenting “was reported to be associated with prolonged overall survival in patients with unresectable cholangiocarcinoma based on 2 small randomized clinical trials [Ortner et al (2003)]29 and Zoepf et al (2005)]30.”75

**Non-Small-Cell Lung Cancer**
NCCN guidelines (v.7.2017) on non-small-cell lung cancer (NSCLC) state that PDT is a treatment option for patients with locoregional recurrence of NSCLC with endobronchial obstruction or severe hemoptysis.1

**National Institute for Health and Care Excellence**
The U.K.’s National Institute for Health and Care Excellence (NICE) has published guidance on a number of applications of PDT.

- Guidance for palliative treatment of advanced esophageal cancer,76 treatment of localized inoperable endobronchial cancer,77 and treatment of advanced bronchial carcinoma78 has indicated that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE guidance has indicated that PDT should be used for the following 3 indications: interstitial photodynamic therapy for malignant parotid tumors,79 early-stage esophageal cancer,80 and bile duct cancer.81
- NICE guidance has indicated that radiofrequency ablation or PDT may be considered for Barrett esophagus with flat HGD, taking into account the evidence of their long-term efficacy, cost, and complication rates.82
- NICE guidance on PDT for brain tumors has indicated that current evidence is limited in quality and quantity, and the procedure should only be used in context of RCTs with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality of life outcomes.83

**Society of Thoracic Surgeons**
The Society of Thoracic Surgeons published practice guidelines on the management of Barrett esophagus with HGD in 2009.84 The guidelines stated that, based on grade B evidence, “photodynamic therapy (PDT) should be considered for eradication of high-grade dysplasia (HGD) in patients at high risk for undergoing esophagectomy and for those refusing esophagectomy’’ and that “it is reasonable to use photodynamic therapy (PDT) to ablate residual intestinal metaplasia after endoscopic mucosal resection (EMR) of a small intramucosal carcinoma in high-risk patients.”
U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00587600</td>
<td>Biomarkers in Phototherapy of Barrett’s Esophagus</td>
<td>208</td>
<td>Sep 2017</td>
</tr>
<tr>
<td>NCT01755013</td>
<td>Open-label Observational Study of Plastic Cylindrical Fiber Optic Diffuser (Pioneer Optics) in Photodynamic Therapy for the Management of Cholangiocarcinoma</td>
<td>55</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02153229</td>
<td>A Randomized Phase 2 Trial of Radical Pleurectomy and Post-Operative Chemotherapy With or Without Intraoperative Porfimer Sodium -Mediated Photodynamic Therapy for Patients With Epitheliod Malignant Pleural Mesothelioma</td>
<td>102</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT03090412</td>
<td>A Randomized Multicenter Phase II Study Using (2-1[Heyloxyethyl]-2-Devinylpyropheophorbide-a) (HPPH) With PDT Versus Standard of Care Surgery for Patients With T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity</td>
<td>114</td>
<td>Nov 2021</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01739465</td>
<td>A Randomized Controlled Trial Comparing Endoscopic Biliary Radiofrequency Ablation With Photodynamic Therapy for Inoperable Cholangiocarcinoma</td>
<td>120</td>
<td>Dec 2015 (unknown)</td>
</tr>
<tr>
<td>NCT02082522a</td>
<td>Multicenter, Open-label, Randomized, Controlled Phase III Clinical Study of the Efficacy and Safety of Photodynamic Therapy Using Porfimer Sodium for Injection as Treatment for Unresectable Advanced Perihilar Cholangiocarcinoma</td>
<td>28</td>
<td>Dec 2018 (terminated)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31641</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)</td>
</tr>
<tr>
<td>43229</td>
<td>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)</td>
</tr>
<tr>
<td>96570</td>
<td>Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)</td>
</tr>
<tr>
<td>96571</td>
<td>Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)</td>
</tr>
<tr>
<td>J9600</td>
<td>Injection, porfimer sodium, 75 mg</td>
</tr>
</tbody>
</table>

**ICD-10 Codes**

- **C15.3-** Malignant neoplasm of esophagus code range
- **C15.9** Malignant neoplasm of bronchus and lung code range
- **C34.00-** Secondary malignant neoplasm of lung code range
- **C34.92** Secondary malignant neoplasm of other and unspecified digestive organs code range
- **D00.1** Carcinoma in situ of esophagus
- **D02.20-** Carcinoma in situ of bronchus and lung code range
- **D02.22**

The following CPT codes may be used to describe endoscopic photodynamic therapy:

- **96570**: Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drugs; first 30 minutes. (List separately in addition to code for endoscopy or bronchoscopy)
- **96571**: as above, but each additional 15 minutes.
As noted in the CPT code description, the procedure will be coded in conjunction with an esophagoscopy or bronchoscopy, which may be coded as follows:

43229: Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesions (includes pre- and post-dilation and guide wire passage, when performed)
31641: Bronchoscopy, rigid or flexible, including fluoroscopic guidance when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)

Claims also may be identified by the use of HCPCS code J9600, describing the drug, porfimer sodium.

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/1/12</td>
<td>New policy; may be considered medically necessary.</td>
</tr>
<tr>
<td>6/1/13</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>4/1/14</td>
<td>Removed deleted code 43228</td>
</tr>
<tr>
<td>4/1/14</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/15</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/16</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/17</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>10/1/17</td>
<td>The Policy statements were changed to include treatment for unresectable cholangiocarcinoma as medically necessary.</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.