Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 10/18/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Photodynamic Therapy for Subfoveal Choroidal Neovascularization, Dermatologic Applications of Photodynamic Therapy and Endoscopic Radiofrequency Ablation or Cryoablation for Barrett’s Esophagus are addressed separately in medical policies 00097, 00098 and 00261, respectively.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider one or more courses of photodynamic therapy (PDT) for oncologic applications to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for photodynamic therapy (PDT) for oncologic applications will be considered when any of the following criteria are met:

- Palliative treatment of obstructing esophageal cancer; or
- Palliative treatment of obstructing endobronchial lesions; or
- Treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy; or
- Treatment of high-grade dysplasia in Barrett’s esophagus; or
- Palliative treatment of unresectable cholangiocarcinoma when used with stenting

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of photodynamic therapy (PDT) for oncologic applications when patient selection criteria are not met to be investigational.*

Based on review of available data, the Company considers other oncologic applications of photodynamic therapy (PDT) including, but not limited to, other malignancies and Barrett’s esophagus without associated high-grade dysplasia to be investigational.*

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Background/Overview
PDT has been investigated for use in a wide variety of tumors, including esophageal, lung, cholangiocarcinoma, prostate, bladder, breast, brain (administered intraoperatively), skin, and head and neck cancers. Barrett esophagus also has 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%. For patients who are not surgical candidates or who refuse surgery and are ineligible for radiotherapy, other ablative techniques (eg, PDT) are options.

Barrett’s Esophagus
The esophagus is normally lined by squamous epithelium. Barrett's esophagus is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium known as intestinal metaplasia, in response to irritation and injury caused by gastroesophageal reflux disease (GERD). Barrett's esophagus occurs in the distal esophagus, may be of any length, focal or circumferential, and can be visualized on endoscopy with a different color than the background squamous mucosa. Confirmation of Barrett's 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’s esophagus are at a 40-fold increased risk for developing this disease compared to the general population. Esophageal adenocarcinoma is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, which results in the phenotypic expression of histologic features of 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. In 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. 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.

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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The indications of the U.S. FDA label for porfimer sodium as of June 2011 are as follows:

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 (NSCLC)
- Treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated

High-grade dysplasia in Barrett’s esophagus
- Treatment of HGD in Barrett’s 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.
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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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
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 PDT for the treatment of precancerous skin conditions, Barrett esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus and skin. The review included literature published through June 2009 and included 88 trials. The authors 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. The authors’ 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 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 is needed. For cholangiocarcinoma, PDT may 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 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 (DFS), may not be relevant in the palliative setting. The prescribing information for porfimer sodium (Photofrin) describes a multicenter, single-arm study of PDT in 17 patients with obstructing esophageal cancer. Patients received from 1 to 3 monthly treatments. Of 17 treated patients, 11 (65%) received clinically important benefit from PDT.
PDT, defined as complete tumor response, normal swallowing, or improvement in dysphagia. After PDT, endoscopic debridement of the esophagus may be required, and residual tumor can be retreated during this process.

A 2014 Cochrane review of treatments for dysphagia in esophageal cancer identified 2 1995 RCTs that compared laser treatment to PDT (total N=278). Results were driven by the larger trial (N=236). In meta-analysis, there was no statistical difference between treatments for improvement in dysphagia. Incidence of fever and photosensitivity was less with laser treatment, and incidence of perforation was less with PDT. However, these estimates were unstable, as evidenced by very wide confidence intervals.

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. The review focused on tumor response and recurrence and disease-specific and overall survival and did not examine quality-of-life outcomes.

In 2011, Rupinski et al reported on a randomized trial of 93 patients with inoperable cancer of the esophagus or esophageal junction who were treated with argon plasma coagulation (APC) alone, APC with PDT, or APC with high-dose rate (HDR) brachytherapy. Both combination therapies were more effective than APC alone in median time to recurrence of dysphagia (85, 59, and 35 days for APC with HDR, APC with PDT, and APC alone, respectively). Overall survival was not significantly different 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**

As for obstructing esophageal tumors, short-term outcomes are relevant for endobronchial tumors. Because laser ablation is commonly used to treat endobronchial lesions, comparative efficacy of PDT and laser ablation is relevant. The Photofrin prescribing information cites 2 studies totaling 211 patients with obstructing endobronchial tumors who were randomized to receive PDT or Nd:YAG laser therapy. Response rates (ie, the sum of complete response [CR] and partial response [PR] rates) for the 2
treatments were similar at 1 week (59% PDT, 58% laser therapy) with a slight increase at 6 weeks for PDT (60% PDT, 41% laser therapy). Clinical improvement, defined as improvements in dyspnea, cough, and hemoptysis, were similar in the 2 groups at 1 week (25%-29%); however, at 1 month or later, 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 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) conducted a small, randomized study to compare PDT and Nd:YAG laser therapy in patients with airway obstruction. Effectiveness 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 only a minimal number of patients with nonobstructing lung cancer 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 radiation therapy. Candidates for PDT are limited to those patients who cannot tolerate surgery or radiation therapy, most commonly due to underlying emphysema, other respiratory disease, or prior radiation therapy. In this primary treatment setting, long-term outcomes such as response rates and DFS are important. The prescribing information for porfimer sodium (Photofrin) describes 3 case series totaling 62 patients with microinvasive lung cancer. Complete tumor response rate, biopsy-proved, at least 3 months after treatment was 50%; median time to tumor recurrence exceeded 2.7 years; median survival was 2.9 years; and disease-specific survival was 4.1 years. In another case series of 95 early-stage lung cancers treated with endoscopic PDT, the CR 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>
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<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>
</tbody>
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<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>N</th>
<th>Results (95% CI)</th>
</tr>
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</table>
| Corti et al (2007) | Early inoperable or recurrent NSCLC | 40 | • CR: 93%  
• 5-y survival: 58%  
Lesion ≥1 cm  
• CR: 58%  
• 5-y survival: 59% |
| Endo et al (2009) | Centrally located early lung cancer; longitudinal tumor length ≤10 mm | 48 | CR: 94%  
5-y survival: 81% |
| FDA (Photofrin prescribing information) (2011) | Microinvasive, inoperable endobronchial tumors | 62 | CR at 3 mo: 50%  
Median survival: 2.9 y (2.1 to 5.7) |


The labeled indication for porfimer sodium suggests that PDT for early-stage lung cancer should be limited to those who are not candidates for either surgery or radiation therapy. However, Cortese et al (1997) reported on a case series of 21 patients with early-stage squamous cell cancer of the lung 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 patients (43%) had a CR at a mean follow-up of 68 months (range, 24-116) and thus were spared surgical treatment.

It should be noted that Nd:YAG laser therapy, electrocautery, and endobronchial brachytherapy also are considered treatment options for early-stage lung cancer. However, unlike obstructing endobronchial lesions, no controlled studies have compared the safety and efficacy of these techniques in early-stage disease.

**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 High-Grade Dysplasia

A 2012 review of endotherapy for Barrett esophagus indicated that although studies have demonstrated long-term success with PDT for the treatment of high-grade dysplasia 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.

The FDA-approved indication for treatment of high-grade dysplasia was based on a multicenter, partially blinded, study that randomized 199 patients to receive porfimer sodium (Photofrin) plus omeprazole or omeprazole alone. Initially, 485 patients with high-grade dysplasia were screened for the trial; 49% were subsequently excluded because high-grade dysplasia 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 CR rate at any one of the endoscopic assessment time points. CR was defined as ablation of all areas of high-grade dysplasia but some areas of low-grade dysplasia or Barrett epithelium may remain. CR 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 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 was significantly more effective than omeprazole alone in eliminating HGD (77% [106/138] vs 39% [27/70], respectively; p<0.001). Patients in the PDT group were approximately half as likely to progress to cancer as those in the omeprazole alone group (15% [21/138] vs 29% [20/70], respectively; p=0.027), with a significantly longer time to progression with PDT. The study is 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-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.

Badreddine et al (2010) performed a retrospective analysis of a cohort of Barrett esophagus patients seen at a specialized Barrett esophagus clinic in the U.S. 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, high-grade dysplasia 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. The authors noted that the possibility of missing prevalent dysplasia despite aggressive surveillance was a limitation of the study.

Pech et al (2008), in a study from Germany, reported long-term (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 5-ALA PDT. (Note: Oral ALA does not have FDA approval.) Fifty-five patients received only PDT, and 13 underwent endoscopic resection and PDT. CR was achieved in 98.5% of patients; during median follow-up of 37 months, recurrences developed in 17% of patients.

Prasad et al (2007) reported similar outcomes for 2 nonrandomized groups patients who received either PDT (n=129) or surgery (n=70) for high-grade dysplasia 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.
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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.

Gao et al (2010) performed a systematic review of the literature on PDT for unresectable cholangiocarcinoma: 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. 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. 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 PDT. 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. 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. Five (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 reproductive 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. 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). 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. 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. 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.
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/cm² 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. 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. 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. 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. 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.
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Soft Tissue Sarcoma
A 2013 retrospective, single-center study from Japan examined PDT in high-grade soft tissue sarcoma. Acidine 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.

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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.

References

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05/02/2013  Medical Policy Committee review
05/22/2013  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014  Medical Policy Committee review
05/21/2014  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015  Medical Policy Committee review
05/20/2015  Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated rationale and references.
05/05/2016  Medical Policy Committee review
05/18/2016  Medical Policy Implementation Committee approval. No change to coverage.
10/01/2016  Coding update
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017  Medical Policy Committee review
05/17/2017  Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017  Medical Policy Committee review
10/18/2017  Medical Policy Implementation Committee approval. Policy statements changed to include treatment for unresectable cholangiocarcinoma as eligible for coverage.
01/01/2018  Coding update
Next Scheduled Review Date:  10/2018

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