Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy #  00234  
Original Effective Date: 03/18/2009  
Current Effective Date: 05/17/2017

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.

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.*

Background/Overview
Photodynamic therapy, also called phototherapy, photoradiotherapy, photosensitizing therapy, or photochemotherapy, is an ablative treatment consisting of administration of a photosensitizing agent and subsequent exposure of tumor cells to a light source of a specific wavelength to induce cellular damage.
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 selectivity for tumor cells occurs through selective retention of photosensitizing agent and selective delivery of light.

Photodynamic therapy 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.

**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.

**Photodynamic Therapy**

Several different photosensitizing agents have been used: 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. ALA is metabolized to protoporphyrin IX, which is preferentially taken up by the mucosa. Clearance of porfimer occurs in a variety of normal tissues over 40–72 hours, but tumors retain porfimer for a longer period. Treatment of Barrett's esophagus may be enhanced by the use of balloons containing a cylindrical diffusing fiber. The balloon is designed to compress the mucosal folds of the esophagus, thus increasing the likelihood that the entire Barrett's 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:
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

**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 February 2015, oral 5-ALA has not received FDA approval for any indication. Topical 5-ALA used for treatment of actinic keratoses is addressed in a separate policy.

This policy 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 in a separate policy.

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**
The most recent update with literature review covered the period through February 11, 2015. Most studies from outside the U.S. use photosensitizing agents that have not been cleared for use in the U.S.

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 randomized controlled trials (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, 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 diseasespecific 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.

In a retrospective study from China (2010), 90 patients with esophageal cancer received PDT with porfimer sodium (n=27), PDT combined with chemotherapy (n=33), or chemotherapy alone (n=30) from 2004 to 2007. Although the incidence of symptomatic palliation (85.2%, 93.9%, and 60.0%, respectively) did not differ statistically across groups, median 2-year survival was statistically different across groups (29.6%, 54.5%, and 16.7%, respectively) (p=0.046).

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.

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. A case series of 100 patients with unresectable lesions also reported successful palliation with PDT. A 2014 RCT comparing neoadjuvant chemotherapy with versus 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 (pulmonaryectomy or lobectomy) compared with patients who did not receive PDT (89% vs 54%; Fisher exact test, \( p=0.002 \) [author calculation]).

**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%.

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.

**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 high-grade dysplasia (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.

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 ablative 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. In 2013, Dunn et al reported an RCT that compared 5-ALA- and porfimer-mediated PDT for the treatment of Barrett esophagus with high-grade dysplasia. Patients were recruited from a single university hospital in London. At 1 year, complete reversal of dysplasia occurred in 16 (47%) of 34 patients randomized to ALA and 12 (40%) of 30 patients randomized to porfimer (Fisher exact test, 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, 1 in the ALA group and 2 in the porfimer group. Overall cancer incidence was 12% and 17% in the ALA and porfimer groups, respectively (p=NSA 4/34 and 5/30). 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 ALA.

Cholangiocarcinoma

There has been 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. 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. Data to compare the efficacy of palliative PDT with other palliative therapies are absent.

Several case series have reported positive quality-of-life outcomes with PDT. Two small randomized studies 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 receive either 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. Pereira et al (2012) reported 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 years follow-up, all but 1 patient had died (5-year overall survival [OS], 3%), most due to disease progression.
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

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 available studies were low to moderate quality. The mean number of subjects was 27 (range, 1-184). Porfimer sodium (Photofrin) was the photosensitizer used in all but 2 of the included studies. The RCTs were discussed earlier.

Kahaleh et al (2008) conducted a retrospective study of 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 chemoradiation therapy. Mortality at 3, 6, and 12 months was 0%, 16%, and 56%, respectively, in the PDT/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 and stenting, and 56 had stenting alone. Median survival was 12 months in the PDT and stenting group versus 6.4 months in the stent-alone group (p<0.01). Patients who received PDT and stenting had lower serum bilirubin levels (p<0.05) and higher Karnofsky Performance Status (p<0.01).

In a 2008 editorial, Baron reviews 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 notes that PDT is not available at all centers and requires expertise in both endoscopy and PDT; laser fibers available in the U.S. 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.”

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 (Roswell Park Cancer Institute). Thirty-two 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 CR (defined as a lack of detectable lesions within the area of treatment). Median time to response was 28 months. Some patients
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

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 age younger than 35 years (mean, 31 years; range, 24-35). The photosensitizing agent was Photogem® (non-FDA-approved) administered intravenously. Mean follow-up from diagnosis was 78 months (range, 8-140). After initial PDT, 12 (75%) of 16 patients showed CR (defined as complete disappearance of adenocarcinoma or hyperplasia on follow-up D&C), and 4 patients were nonresponders. Four (33%) of the 12 initial responders recurred 6 months after CR; 2 responded after additional PDT treatments. One of 4 initial nonresponders achieved CR after a second PDT treatment. Seven patients attempted to become pregnant, all initial responders. Four patients (57%) had 7 pregnancies, 4 with artificial reproductive technology and 3 by natural means, resulting in 6 live births. All deliveries were by cesarean section. 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, age 45 years or younger at diagnosis of early-stage (90% IA1 or IB1) cervical cancer who underwent 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 patient (5%) relapsed. Ten (77%) of 13 patients who attempted pregnancy were successful; live birth occurred in 7 cases, 5 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). Criteria for PDT efficacy varied across studies, but most (10/14) required biopsy. Overall, CR rate ranged from 0% to 100%. Two small RCTs (total N=60) and 1 small case-control study (N=22) found no difference in CR rate between PDT versus placebo, PDT with hexylaminolevulinate (HAL) versus PDT with methylaminolevulinate, or PDT versus conization. Seven studies (total N=319) reported human papillomavirus (HPV) eradication rate, which ranged from 53% to 80%.

In 2014, Hillemanns et al reported on an international RCT of HAL-PDT 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 CIN1 and 83% with CIN2 had oncogenic HPV infection. Statistically significant differences in CR at 3 months compared with placebo were observed only for patients with CIN2 who received 5% HAL (18 [95%] of 19 patients vs 12 [57%] of 21 patients; Fisher exact test, 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 is 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 et al 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, 6 by “normal delivery” and 2 by cesarean delivery.

Subsequent to the Tao et al systematic 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, hexaminolevulinate or methylaminolevulinate (neither FDA-approved for systemic use). The primary end point was CR at 6 months, defined as normal histology and cytology. Women treated with hexaminolevulinate 40 mM applied twice in 3 hours (vs 12 hours) followed by a light dose of 50 to 100 J/cm³ had the best response, with response rate of 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 before changes are made to the policy statement.

**Bladder Cancer**

Investigators in Germany and Korea examined cohorts with non-muscle-invasive bladder cancer who were 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 DFS was 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 at 12, 24, and 30 months was 91%, 64%, and 60%, respectively.

**Head and Neck Cancers**

A 2013 systematic review from The Netherlands reported on metatetra (hydroxyphenyl)chlorin (mTHPC Foscan®; non-FDA-approved)-mediated PDT of squamous cell carcinoma in the head and neck. Twelve studies met inclusion criteria for the review. Six reported on PDT with curative intent and 6 for palliative treatment. Data from 4 studies reporting on curative therapy were pooled (n=301). The authors concluded that data are insufficient to permit conclusions on PDT for curative intent and that randomized trials are needed. Palliative therapy appears to increase quality of life by approximately 30% at 4 months, as measured by the University of Washington Quality of Life Questionnaire scale and the Quality of Life
Several small, uncontrolled studies subsequently reported on PDT for laryngeal, oral, and nasopharyngeal cancers.

- At a single U.S. center, Silbergleit et al (2013) applied PDT to 8 adults (mean age, 66 years; range, 49-79) who had Tis (n=6) or T1N0M0 (n=2) squamous cell carcinoma of the larynx to a maximum depth of 1 mm. Measures of vocal cord function (vibration amplitude and mucosal wave function) were assessed at baseline and for at least 20 weeks after treatment. By week 20, all posttreatment measures on the tumor side improved compared with pretreatment values and approached pretreatment values on the nontumor side. Vocal quality was not assessed.

- Wildeman et al (2013) reported on 7 patients with nonmetastatic nasopharyngeal carcinoma who were treated at a single university hospital in Indonesia, where nasopharyngeal carcinoma is among the most common cancers. All patients had received radiation therapy plus chemotherapy and received PDT for local persistent disease (n=6) or local recurrence (n=1). All patients achieved CR 12 weeks after PDT; 3 patients subsequently developed regional recurrence, and 1 patient died.

- At a single center in France, Durbec et al (2013) applied mTHPC-mediated PDT to 15 adults (mean age, 63 years; range, 52-92) with locally recurrent oral or oropharyngeal carcinoma to a maximum depth of 1 cm. All patients were ineligible for repeat external radiotherapy. Fourteen patients (93%) achieved CR with PDT, and 1 patient achieved PR. Median recurrence-free survival was 12 months (range, 3-74). At mean follow-up of 29 months, estimated recurrence-free and OS was 52% and 72%, respectively, at 1 year, and 34% and 36%, respectively, at 5 years.

- At a single U.S. center, Rigual et al (2013) applied intraoperative PDT to 15 patients with primary or recurrent, early-stage or advanced, head and neck squamous cell carcinomas. A novel photosensitizing agent (2-[1-hexyloxyethyl]-2-devinylpyropheophorbide-a [HPPH]), developed by the investigators, was used. At 48-month follow-up, 5 patients had died (4-year OS, 67%), and 3 of 10 surviving patients had progressed (4-year PFS, 47%).

- A U.S. cancer center enrolled 30 patients in a 2009 study to determine efficacy and safety of Photofrin PDT for primary or recurrent moderate-to-severe oral or laryngeal dysplasia, CIS, or T1N0 carcinoma. Twenty patients (67%) had a CR, 1 (30%) had a PR, and 1 (30%) had no response. Three patients with oral dysplasia with an initial CR experienced recurrence. All patients with no response, PR, or recurrence after initial response underwent salvage treatment. No patient required airway intervention, and all complications resolved without permanent sequelae.

- A 2010 retrospective review of 30 patients with early-stage (TisT2N0M0) squamous cell carcinoma of the oral cavity and oropharynx who were treated with Photofrin PDT found that 24 patients (80%) achieved CR (follow-up, 3-144 months). Six patients who had PR with recurrence were subsequently treated with conventional therapy. Eleven of 24 patients (46%) were cancer-free at 2 years after PDT.

In a 2007 review, Biel reported his own experience with 276 patients treated with Photofrin PDT for early oral and laryngeal cancers over a period of nearly 16 years and summarized previously published small
case series. Of 115 patients in the author’s series who had recurrent or primary carcinoma-in-situ (CIS), T1N0 and T2N0, 5-year cure rate was 100%; at mean follow-up of 91 months, there were 10 recurrences. For 113 patients with recurrent or primary CIS 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. Three-year cure rate was 100% (mean follow-up 56 months). These data require replication in larger, comparative trials.

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 for 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 DFS (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).

In 2009, Wildeman et al reviewed evidence for the efficacy of PDT in patients with recurrent nasopharyngeal carcinoma. Of 5 included studies, one was a series of 135 patients with reported CR in 76 cases and marked response in 47 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. A U.S. cancer center enrolled 30 patients in a trial to determine efficacy and safety of Photofrin PDT for primary or recurrent moderate to severe oral or laryngeal dysplasia, CIS, or T1N0 carcinoma. Twenty patients (67%) had a CR, 1 (30%) had a PR, and 1 (30%) had no response. Three patients with oral dysplasia with an initial CR experienced recurrence. All patients with no response, PR, or recurrence after initial response underwent salvage treatment. No patient required airway intervention, and all complications resolved without permanent sequelae.

Section Summary
Evidence for PDT in head and neck cancers comprises primarily small cohort studies of mixed cancer type (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 treatment of mesothelioma also has 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.
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

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 (approximately 50% glioblastoma). The photosensitizing agent was talaporfin sodium (Laserphyrin®; non-FDA-approved). At 6 months, 2 patients had local progression (6-month PFS, 91%); at 1 year, 1 patient had died (1-year OS, 95.5%). Median PFS 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 Photofrin PDT 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, 1 died of unrelated cause, and 6 were free of brain disease until death. Two of the remaining patients (1 with metastatic bowel cancer and 1 with unknown primary) died of local brain recurrence. A review of the literature on PDT applications in brain tumors relied largely on unpublished data and was not reviewed for this policy.

Prostate Cancer
PDT has been used for the management of prostate cancer. Two single-center studies from France used PDT in men with low-risk prostate cancer. In both studies, the photosensitizing agent was padeliporfin (Tookad®; not FDA-approved). Barret et al (2013) reported a retrospective study of 23 men with clinically localized prostate cancer who were treated with PDT at a single center in France. All men had Gleason score of 6. At a median of 9 months’ follow-up, there was no change from baseline in median International Prostate Symptom Score (6 at both time points indicating mild urinary symptoms). Median score on the International Index of Erectile Function-5 worsened from 23, indicating no erectile dysfunction, to 13, indicating mild to moderate erectile dysfunction. Eymert-Morin et al (2013) reported on 56 patients who had participated in a randomized padeliporfin dose-finding trial. Cancer ablation in treated lobes was observed in 38 (68%) patients.

In a review of focal treatments for prostate cancer, Kasivisvanathan et al (2013) suggested that because PDT requires oxygen to produce free oxygen radicals, it may not be effective in hypoxic prostate tumors.

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 (log-rank test, p=0.75) or 10-year local recurrence (p=0.36).

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

Ongoing Clinical Trials
A search of online site ClinicalTrials.gov in February 2015 identified:
Two active phase 2/3 trials for the treatment of cholangiocarcinoma:
  - An RCT of PDT versus radiofrequency ablation for inoperable cholangiocarcinoma (NCT01739465)
  - An RCT of PDT for palliation of inoperable cholangiocarcinoma; estimated completion is December 2015 (NCT01755013)

Two active phase 3 trials for the treatment of prostate cancer; both use a novel drug in development, padeliporfin (Tookad), as the photosensitizing agent:
  - An RCT comparing PDT with active surveillance for localized prostate cancer (NCT01310894)
  - A single-arm quality-of-life study for patients with localized prostate cancer who were treated with Tookad-mediated PDT (NCT01875393)

Additionally:
  - A phase 2/3 trial will evaluate whether the presence or absence of biomarkers in Barrett esophagus influences outcomes with PDT or radiofrequency ablation (NCT00587600).
  - A phase 3 RCT will compare surgery, radiation therapy, and chemotherapy with or without PDT for the treatment of newly diagnosed or recurrent malignant brain and central nervous system tumors (NCT00003788).

Summary
Photodynamic therapy is an ablative treatment consisting of administration of a photosensitizing agent and subsequent exposure of tumor cells to a light source of a specific wavelength to induce cellular damage. After administration of a photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques.

In general, the evidence to assess the role of PDT in the treatment of malignancies and Barrett esophagus is of limited quality but suggests that PDT may be useful for palliative treatment of obstructing esophageal cancer and endobronchial lesions. PDT for treatment of early-stage NSCLC has shown benefit and may be used to improve quality of life for patients who are ineligible for surgery and radiation therapy. PDT also may be considered for treatment of HGD in Barrett esophagus, as controlled and uncontrolled studies have demonstrated favorable CR rates with the use of PDT. However, radiofrequency ablation and endoscopic mucosal resection appear to be replacing PDT as preferred methods of ablation for in Barrett esophagus.

Data on use of PDT for other malignancies and Barrett esophagus without high-grade dysplasia are limited. The published literature generally comprises small case series without comparator groups. Evidence for efficacy of photodynamic therapy for palliative treatment of unresectable cholangiocarcinoma is accumulating; however, RCTs are needed to confirm its utility compared with alternative treatments such as chemoradiation. Thus, the use of PDT for other malignancies and Barrett esophagus without HGD is considered investigational because the impact on health outcomes is unknown.

References
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017


Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017


Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017


Policy History

Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

03/04/2009 Medical Director review
03/18/2009 Medical Policy Committee approval. New policy.
03/05/2010 Medical Policy Committee approval
03/19/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2011 Medical Policy Committee review
03/16/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2012 Medical Policy Committee review
03/21/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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.

Next Scheduled Review Date: 05/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA
Oncologic Applications of Photodynamic Therapy, Including Barrett’s Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 05/17/2017

disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>31641, 43229, 96570, 96571</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J9600</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>C15.3-C15.9, C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92, C49.A0-C49.A2, C78.00-C78.02, C78.7-C78.89, D00.1-D00.2, D02.20-D02.22</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.