Name of Policy: 
Oncologic Applications of Photodynamic Therapy, Including 
Barrett’s Esophagitis

Policy #: 337 
Category: Medical 
Latest Review Date: March 2014 
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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.
**Description of Procedure or Service:**
Photodynamic therapy (PDT), also called phototherapy, photoradiation therapy, 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 a combination of selective retention of photosensitizing agent and selective delivery of light.

Photodynamic therapy has been investigated for use in a wide variety of tumors, including cholangiocarcinoma and esophageal, 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 by the endoscopist as being 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 to carcinoma. Most patients with nondysplastic Barrett’s esophagus do not progress past non-dysplasia. Nondysplastic Barrett’s esophagus progresses to high-grade dysplasia at a rate of 0.9% per patient, per year. Progression of low-grade to high-grade dysplasia has been reported as 6%–28%. Once high-grade dysplasia is present, the risk of developing adenocarcinoma is 2%–10% per patient, per year, and approximately 40% of patients diagnosed with high-grade dysplasia by 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 four to six 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 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.

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The indications of the U.S. Food and Drug Administration (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 high-grade dysplasia in Barrett's esophagus who do not undergo esophagectomy

As of February, 2014, oral 5-ALA has not yet received FDA approval for any indication. Topical 5-ALA is used for the treatment of actinic keratosis and is addressed in policy #050.

This policy only addresses the oncologic applications of photodynamic therapy and does not address its use as a treatment of actinic keratosis (see policy #050) or age-related macular degeneration (see policy #047). In addition, photodynamic therapy 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 (see policy #028).
**Policy:**
One or more courses of photodynamic therapy meets Blue Cross and Blue Shield’s medical criteria for coverage for any of the following oncologic applications:

- 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

**Other oncologic applications of photodynamic therapy** including, but not limited to, other malignancies and Barrett's esophagus without associated high-grade dysplasia do not meet Blue Cross and Blue Shield’s medical criteria for coverage and are considered investigational.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
The most recent update with literature review covered the period through February, 2014. 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 photodynamic therapy (PDT) for the treatment of precancerous skin conditions, Barrett esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus and skin. 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 or improvement in swallowing. Long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting. The product insert for Photofrin describes a multicenter, single-arm study of the use of photodynamic therapy in 17 patients with obstructing esophageal cancer. Patients received from one to three monthly treatments of photodynamic therapy. Of the 17 treated patients, 11 (65%) received clinically important benefit from photodynamic therapy, 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.

McCann et al reported on a systematic review of traditional non-endoscopic and endoscopic treatments for early esophageal cancer, including 26 PDT studies. The reviewers noted the lack of evidence from large, randomized trials and found the quality of evidence available overall was generally low. While the evidence did demonstrate that endoscopic techniques reduced morbidity and mortality compared to esophagectomy, outcomes from endoscopic treatments were similar, and no single endoscopic technique could be 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.

Rupinski et al reported on a randomized study of 93 patients with inoperable cancer of the esophagus or esophageal junction to compare argon plasma coagulation (APC) alone to PDT with APC or high-dose rate brachytherapy (HDR) with APC. Both combination therapies were more effective than APC alone in median time to recurrence of dysphagia (85, 59, and 35 days for HDR with APC, PDT with APC, 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 by Li et al (2010), 909 patients with esophageal cancer underwent photofrin PDT (n=27), PDT combined with chemotherapy (n=33) or chemotherapy alone (n=30) from 2004 – 2007. Rates of symptomatic palliation (85.2%, 93.9%, and 60%, respectively) were not significantly different. The differences in median survival rate at two years were statistically significant (29.6%, 54.5% and 16.7%, respectively) (p=0.046).

Obstructing Endobronchial Tumors
As for obstructing esophageal tumors, short-term outcomes are also relevant for photodynamic therapy as a treatment of 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 two studies totaling 211 patients with obstructing endobronchial tumors who were randomized to receive photodynamic therapy or Nd:YAG laser therapy. Response rates (i.e., the sum or complete response [CR] and partial response [PR] rates) for the two treatments were similar at one week (59% photodynamic therapy, 58% laser therapy) with a slight increase in response rates for PDT at six weeks (60% photodynamic therapy, 41% laser therapy). Clinical improvement, as evidenced by improvements in dyspnea, cough, and hemoptysis, were similar in the two groups at one week (25%-29%); however, at one month or later, 40% of patients treated with photodynamic therapy reported clinical
improvement compared to 27% treated with laser therapy. Due to missing data in the studies, statistical comparisons were not performed.

In another small, published, randomized study comparing photodynamic therapy and Nd:YAG laser therapy in patients with airway obstruction, Diaz-Jimenez et al reported that the two techniques had similar effectiveness over a 24-month period. The authors noted a better immediate response rate associated with laser therapy than with PDT, suggesting that laser therapy may be particularly appropriate for those requiring rapid relief of symptoms. Results of a larger case series of 100 patients with unresectable lesions also report that photodynamic therapy is associated with successful palliation.

Similar to treatment of obstructing esophageal lesions, repeat endoscopy may be required for tumor debridement, at which time repeat photodynamic therapy may be performed to treat residual tumor.

**Early-Stage Lung Cancer**

It is anticipated that only a minimal number of patients with non-obstructing lung cancer will be appropriate candidates for photodynamic therapy. 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 photodynamic therapy 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 disease-free survival are important. The product insert for Photofrin also refers to 3 case series totaling 62 patients with microinvasive lung cancer. The complete tumor response rate, biopsy-proved, at least three months after treatment was 50%, median time to tumor recurrence was more than 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, the complete response 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 reported on a case series of 21 patients with early-stage squamous cell cancer of the lung who were offered photodynamic therapy as an alternative to surgery. Patients were followed up closely with repeat endoscopy, with surgical resection if cancer persisted after no more than two courses of photodynamic therapy. A total of nine patients (43%) had a complete response at a mean follow-up of 68 months (range 24-116 months) and thus were spared surgical treatment.

It should be noted that Nd:YAG laser therapy, electrocautery, and endobronchial brachytherapy are also 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.
Barrett's 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-labeled indication for treatment of high-grade dysplasia is based on a multicenter, partially blinded, study that randomized 199 patients to receive either 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 package insert, the high patient exclusion rate re-enforces the recommendation by the American College of Gastroenterology that the diagnosis of dysplasia in Barrett's esophagus be confirmed by an expert gastrointestinal pathologist. Patients randomized to the treatment group received up to three courses of photodynamic therapy separated by 90 days. The primary efficacy endpoint was the complete response rate at any one of the endoscopic assessment time points. Complete response was defined, at a minimum, as ablation of all areas of high-grade dysplasia but with some areas of low-grade dysplasia. A total of 76.8% of patients in the treatment group achieved a complete response compared to 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. 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 three months until four consecutive quarterly biopsy results were negative for HGD and then biannually until 60 months after randomization or until treatment failure. At five 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 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, in a study from Germany, reported long-term (five-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 (greater than 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-aminolevulinic acid (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 reported similar outcomes for two 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 one 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’s exact test, p=0.62). With median follow-up of two years, three prevalent cancers occurred in each group within 12 months of treatment, and three incident cancers occurred more than 12 months after treatment, one in the ALA group and two in the porfimer group. Overall cancer incidence was 12% and 17% in the ALA and porfimer groups, respectively (p=SISA 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 research 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 results, as measured by quality of life studies. Two small randomized studies have reported both palliative effects and an increase in median survival. For example, Ortner et al conducted a trial of 39 patients with nonresectable cholangiocarcinoma who were randomized to receive either endoscopic stenting alone or in conjunction with PDT. The median survival of the 20 patient in the PDT group was 493 days compared to 98 days in the 19 patients who underwent stenting alone. The trial was terminated prematurely due to the favorable results. Zoepf et al randomized 32 patients with
cholangiocarcinoma to stenting with and without PDT. Median survival for the PDT group was 21 months compared to seven months in the control group. Pereira et al reported a prospective cohort study of 34 patients with unresectable cholangiocarcinoma who were treated with porfimer-mediated PDT at three centers in England. Median survival was approximately 13 months with or without chemotherapy. At five years follow-up, all but one patient had died (five-year overall survival [OS], 3%), most due to disease progression.

Gao et al performed a systematic review of the literature on PDT for unresectable cholangiocarcinoma. Two RCTs, two comparative trials with concurrent controls, one comparative trial with historical controls, and 15 case series were included. The two 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 two of the included studies. The RCTs were discussed earlier.

Kahaleh et al 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 three, six, 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 analyzed records of 184 patients treated over a ten-year period in Germany for hilar cholangiocarcinoma. Sixty patients underwent resection (eight 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 post-treatment photosensitivity lasts for four to six 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 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 (nine cervical, six vulvar, six vaginal, five ovarian, five endometrial, and one 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 received more than one treatment. Patients with vaginal and cervical recurrences also had moderate to severe burning sensation, with maximum treatment for three weeks.

In a retrospective Korean cohort study, Choi et al 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 four patients were nonresponders. Four (33%) of the 12 initial responders recurred six months after CR; two responded after additional PDT treatments. One of four initial nonresponders achieved CR after a second PDT treatment. Seven patients attempted to become pregnant, all initial responders. Four patients (57%) had seven pregnancies, four with artificial reproductive technology and three by natural means, resulting in six live births. All deliveries were by cesarean section. No evidence of endometrial cancer recurrence or hyperplasia was found before or after childbirth.

Soergel et al reported on 72 patients with histologically confirmed cervical intraepithelial neoplasia (CIN) Grade 1, 2, or 3 who were treated with PDT at a single center in Germany. Patients were randomized to one of six 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 six months, defined as normal histology and cytology. Women treated with hexaminolevulinate 40 mM applied twice in three hours (versus 12 hours) followed by a light dose of 50-100 J/cm3 had the best response, with response rate of 83% among women with CIN grade 2. Groups were not powered for statistical comparison.

Istomin et al reported on 112 patients with morphologically proven cervical intraepithelial neoplasia grades 2 and 3 with at least one 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 human papillomavirus (HPV), 47 (53%) had complete eradication of HPV infection three months after treatment.

Winters et al reported on a Phase 2 European study of imiquimod and PDT for vulval 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 nonmuscle-invasive bladder cancer who were treated with PDT after transurethral resection of the bladder. Bader et al applied intravesical hexaminolevulinate (Hexvix®) and bladder wall irradiation to 17 patients with intermediate- or high-risk urothelial cell carcinoma. Hexaminolevulinate, marketed as Cysview®, is FDA-approved for photodynamic detection of bladder cancer. Six-month, nine-month, and 21-month disease-free survival was 53%, 24%, and 12%, respectively. Lee et al 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 six for palliative treatment. Data from four 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 four months, as measured by the University of Washington Quality of Life Questionnaire scale and the Quality of life questionnaire (QLQ) on head and neck cancer of the European Organization for Research and Treatment of Cancer.

Several small, uncontrolled studies subsequently reported on PDT for laryngeal, oral, and nasopharyngeal cancers.

- At a single U.S. center, Silbergleit et al applied PDT to eight 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 post-treatment 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 reported on seven 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; three patients subsequently developed regional recurrence, and one patient died.

- At a single center in France, Durbec et al 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 one 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 one year, and 34% and 36%, respectively, at five years.

- At a single U.S. center, Rigual et al 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 months’ follow-up, five patients had died (four-year OS, 67%), and three of ten surviving patients had progressed (four-year PFS, 47%).

At a single center in The Netherlands, Karakullukcu et al 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 5mm. 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 five-year disease-free survival (47% vs 53% in the PDT and surgery groups, respectively; Cox proportional hazard, p=0.75), five-year local recurrence-free survival (67% vs 74%; p=0.13), or OS (83% vs 75%; p=0.17).

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, five-year cure rate was 100%; at mean follow-up of 91 months, there were ten recurrences. For 113 patients with recurrent or primary CIS and T1N0 squamous cell carcinoma of the oral cavity, there were six recurrences within eight months of initial treatment salvaged with either repeat PDT or surgical resection. Two patients with T1 tongue tumors developed positive regional lymph nodes within three months of PDT, had conventional neck dissection, and were disease-free for at least five years. In 48 patients treated for superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity, there were five 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.

In 2009, Wildeman et al reviewed evidence for the efficacy of PDT in patients with recurrent nasopharyngeal carcinoma. Of five 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 four 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, one (30%) had a PR, and one (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 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 two years after PDT.

**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.

**Brain Cancer**
At two university hospitals in Japan, Muragaki et al 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 six months, two patients had local progression (six-month PFS, 91%); at one year, one patient had died (one-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 used intraoperative Photofrin® PDT in 14 patients with metastatic brain cancer (seven originating in the lung and seven 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 and one 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 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 six. At a median of nine months’ follow-up, there was no change from baseline in median International Prostate Symptom Score (six at both time points indicating mild urinary symptoms). Median score on the International Index of Erectile Function-five worsened from 23, indicating no erectile dysfunction, to 13, indicating mild to moderate erectile dysfunction. Eymerit-Morin et al 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 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 ten-year overall survival (log-rank test, p=0.75) or ten-year local recurrence (p=0.36).

Other Applications
PDT 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.

Summary
Photodynamic therapy (PDT) 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.

In general, the evidence to assess the role of PDT in the treatment of malignancies and Barrett’s 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 non-small cell lung cancer has shown benefit and may be used to improve quality of life for patients who are ineligible for surgery and radiation therapy. PDT may also be considered for treatment of high-grade dysplasia in Barrett’s esophagus, as controlled and uncontrolled studies have demonstrated favorable complete response rates with the use of PDT. However, radiofrequency ablation and endoscopic mucosal resection appear to be replacing PDT as the preferred methods of ablation for high-grade dysplasia in Barrett’s esophagus.

Data on use of PDT for other malignancies and Barrett’s esophagus without high-grade dysplasia are limited. The published literature consists of generally small case series without comparator groups. Evidence for efficacy of photodynamic therapy for palliative treatment of unresectable cholangiocarcinoma is accumulating; however, randomized controlled trials are needed to confirm its utility compared to alternative treatments such as chemoradiation. Thus, the use of PDT for other malignancies and Barrett’s esophagus without high-grade dysplasia is considered investigational because the impact on health outcomes is not known.

Practice Guidelines and Position Statements
ACCP
The 2007 American College of Chest Physicians practice guidelines on bronchial intraepithelial neoplasia and early central airways lung cancer recommend PDT as a treatment option for superficial squamous cell carcinoma in patients who are not surgical candidates. The ACCP guidelines also note that there is limited experience in the use of PDT in patients who are candidates for surgery.
STS
The Society of Thoracic Surgeons published practice guidelines for the management of Barrett’s esophagus with high-grade dysplasia in June 2009. The guideline states that, based on grade B evidence, “photodynamic therapy (PDT) should be considered for eradication of high-grade dysplasia (HGD) in patients at high risk for undergoing esophagectomy and for those refusing esophagectomy” and that “it is reasonable to use photodynamic therapy (PDT) to ablate residual intestinal metaplasia after endoscopic mucosal resection (EMR) of a small intramucosal carcinoma in high-risk patients”.

AGA
The 2011 American Gastroenterological Association’s position statement on Barrett's esophagus management recommends photodynamic therapy as an option for treatment of confirmed high-grade dysplasia with Barrett’s esophagus.

NCCN
Esophageal Cancer and Barrett Esophagus
The National Comprehensive Cancer Network (NCCN) guideline on esophageal cancer lists photodynamic therapy as an ablative method for patients with Barrett’s esophagus with high-grade dysplasia, and for palliation of dysphagia in patients with esophageal cancer. Endoscopic mucosal resection (EMR) and ablation for T1a tumors and EMR or ablation for tumor in situ are listed as treatment options for Barrett’s esophagus and high-grade dysplasia.

Cholangiocarcinoma
NCCN lists ablation (PDT is an ablative technique) as a treatment option in patients with microscopic margins (R1) or residual local disease (R2) post-resection of intrahepatic cholangiocarcinoma. NCCN describes PDT as a relatively new therapy for the local treatment of unresectable cholangiocarcinoma saying that the combination of PDT and biliary stenting “has been shown to significantly improve the overall survival of patients with unresectable cholangiocarcinoma based in two small randomized clinical trials”.

Non-Small Cell Lung Cancer
The NCCN guideline on non-small cell lung cancer states that PDT is a treatment option in patients with locoregional recurrence of non-small cell lung cancer with endobronchial obstruction or severe hemoptysis.

The UK’s National Institute for Health and Clinical Excellence (NICE) has published guidance on a number of applications of PDT.

- Guidance for palliative treatment of advanced esophageal cancer, treatment of localized inoperable endobronchial cancer, and treatment of advanced bronchial carcinoma state that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE states that PDT should be used only with special arrangements for clinical governance, consent, and audit for the following four indications: interstitial photodynamic therapy for malignant parotid tumors, early-stage esophageal cancer, bile duct cancer, and high-grade dysplasia in Barrett’s esophagus.
• NICE guidance on PDT for brain tumors states that current evidence is limited in quality and quantity, and the procedure should only be used in context of randomized controlled trials with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality-of-life outcomes.

**Key Words:**
Hematoporphyrin, Oncologic Applications of Photodynamic Therapy; Photochemotherapy, Photodynamic Therapy, Photodynamic Therapy, Oncologic Applications, Photofrin®, Photoradiation Therapy, Photosensitizing Therapy, PDT, NPc6, Foscan, metatetrahydroxyphenylchlorin

**Approved by Governing Bodies:**
The indications of the U.S. Food and Drug Administration (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 high-grade dysplasia in Barrett’s esophagus who do not undergo esophagectomy

As of February 2014, oral 5-ALA has not yet received FDA approval for any indication. Topical 5-ALA as used for treatment of actinic keratoses is addressed in a separate policy.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Lowe’s Precertification Requirement—**Effective for dates of service on or after February 1, 2010** please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of
Alabama’s medical policy does not apply for Lowe’s members for dates of service on or after February 1, 2010. This policy was in effect for Lowe’s prior to February 1, 2010.

**Coding:**

CPT codes:

- **31641** Bronchoscopy (rigid or flexible); with destruction of tumor or relief of stenosis by any method other than excision
- **43228** Esophagoscopy, rigid or flexible; with ablation of tumor(s), polyp(s), or other lesions not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
- **96570** Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via application of photosensitive drug(s); first 30 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
- **96571** Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via application of photosensitive drug(s); each additional 15 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
- **J9600** Porfimer Sodium, 75 mg

**References:**

76. www.clinicaltrials.gov.

Policy History:
Medical Policy Group, January 2009 (4)
Medical Policy Administration Committee, February 2009
Available for comment February 6-March 23, 2009
Medical Policy Group, March 2010 (3)
Medical Policy Group, June 2011; Updates to Key Points & References
Medical Policy Group, March 2012 (3): Updated Key Points & References
Medical Policy Panel, March 2013
Medical Policy Group, April 2013 (3): Updated Key Points & References; no change in policy statement
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 (3): 2014 Updates to Description, Key Points, Governing Bodies & References; no change in policy statement
Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link. Transfer to CareCore is on hold until further notice. The policy has been returned to FINAL.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.