Oncologic Applications of Photodynamic Therapy, including Barrett’s Esophagus

Description

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. Tumor selectivity in treatment occurs through a combination of selective retention of photosensitizing agent and selective delivery of light.

Background

Photodynamic therapy (PDT) has been investigated for use in a wide variety of tumors, including esophageal cancer, cholangiocarcinoma, prostate, 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 nondysplasia. Nondysplastic Barrett’s
esophagus progresses to high-grade dysplasia at a rate of 0.9% per patient, per year. (1) Progression of low-grade to high-grade dysplasia has been reported as 0.5-13.4% per patient year. (2) 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. (1)

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.

Regulatory Status

The indications of the U.S. Food and Drug Administration (FDA) label for porfimer sodium as of June 2011 are as follows (3):

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 patients who do not undergo esophagectomy

As of February 2014, 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. (Policy No.2.01.44)
This policy addresses only the non-dermatologic 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 not addressed in this policy.

**Related policies**

2.01.44 Dermatologic Applications of Photodynamic Therapy
2.01.80 Endoscopic Radiofrequency Ablation or Cryoablation for Treatment of Barrett’s Esophagus
9.03.08 Photodynamic Therapy for Choroidal Neovascularization.

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

One or more courses of photodynamic therapy may be considered **medically necessary** for the following oncologic applications:

- palliative treatment of obstructing esophageal cancer
- palliative treatment of obstructing endobronchial lesions
- treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy
- treatment of high-grade dysplasia in Barrett’s esophagus
- treatment of cholangiocarcinoma

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

**Rationale**

Evidence for PDT for oncologic applications identified through literature searches conducted for development of this policy is summarized below. Much of the recent literature from outside the U.S. reports experience with photosensitizing agents that have not been cleared for use in the U.S.

Fayter and others produced a systematic review of PDT in the treatment of pre-cancerous skin conditions, Barrett’s esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus and skin published in 2010 for the Health Technology Assessment (HTA) program of the United Kingdom’s National Institute for Health Research (NIHR). (1) The review included literature published through June 2009 and included 88 trials. The authors note a number of limitations in the body of evidence including that there were few well-conducted, adequately powered randomized controlled trials (RCTs), and methodologic limitations and gaps in the evidence base make drawing
firm conclusions difficult. The authors’ conclusions are summarized as follows: for Barrett’s 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 when 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 (DFS), may not be relevant in the palliative setting. The product insert for porfimer sodium (Photofrin) describes a multicenter, single-arm study of the use of PDT in 17 patients with obstructing esophageal cancer. (4) Patients received from 1 to 3 monthly treatments of PDT. Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT, defined as complete tumor response, normal swallowing, or improvement in dysphagia. Endoscopic debridement of the esophagus may be required after the PDT. At that time, the residual tumor can also be retreated.

A 2014 Cochrane review of treatments for dysphagia in esophageal cancer identified 2 1995 RCTs that compared laser treatment to PDT (total N=278). (5) 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 and colleagues, in 2011, reported on a systematic review of traditional non-endoscopic and endoscopic treatments for early esophageal cancer, including 26 PDT studies. (6) 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.

In 2011, Rupinski and colleagues 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. (7) 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 PDT with APC and APC alone groups than the HDR with APC group.

In a retrospective study from China, 90 patients with esophageal cancer underwent photofrin PDT (n=27), PDT combined with chemotherapy (n=33), or chemotherapy alone (n=30) from 2004 to
2007. (4) Rates of symptomatic palliation (85.2%, 93.9%, and 60.0%, respectively) were not significantly different. The differences in median survival rate at 2 years were statistically significant (29.6%, 54.5%, and 16.7%, respectively) (p=0.046)

Obstructing Endobronchial Tumors

Similar to obstructing esophageal tumors, short-term outcomes are also relevant for PDT as a treatment of endobronchial tumors. Laser ablation is commonly used to treat endobronchial lesions, and, thus, the relative efficacy of PDT and laser ablation is also relevant. The product insert cites 2 studies totaling 211 patients with obstructing endobronchial tumors who were randomized to receive PDT or Nd:YAG laser therapy. (4) The response rates (i.e., the sum or 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 in response rates for PDT at 6 weeks (60% PDT, 41% laser therapy). Clinical improvement, as evidenced by 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 to 27% treated with laser therapy. Due to missing data in the studies, statistical comparisons were not performed.

Diaz-Jimenez et al (1999) conducted a small, randomized study to compare PDT and Nd:YAG laser therapy in patients with airway obstruction. (8) 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 1999 case series of 100 patients with unresectable lesions also reported successful palliation with PDT. (9) 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 to patients who did not receive PDT (89% vs 54%; Fisher exact test, p=0.002 [author calculation]). (10)

Early-Stage Lung Cancer

It is anticipated that only a minimal number of patients with non-obstructing 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 product insert for porfimer sodium (Photofrin) also refers to 3 case series totaling 62 patients with microinvasive lung cancer. (4) The complete tumor response rate, biopsy-proved, at least 3 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. (1) In another case series of 95 early-stage lung cancers, the CR rate was 83.2%. (11)

The labeled indication 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 and colleagues
reported on a case series of 21 patients with early-stage squamous cell cancer of the lung and who were offered PDT as an alternative to surgery. (12) Patients were followed up closely with repeat endoscopy, with surgical resection if cancer persisted after no more than 2 courses of PDT. A total of 9 patients (43%) had a CR 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 review of endotherapy for Barrett’s esophagus, published in 2012, indicates that while studies have demonstrated the long-term success of PDT for the treatment of high-grade dysplasia in Barrett’s esophagus, its disadvantages have limited its continued use compared to newer modalities. (13) The cited limitations of PDT include photosensitization, stricture formation, buried glands that harbor neoplastic potential, and decreased efficacy compared to 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 porfimer sodium (Photofrin) plus omeprazole or omeprazole alone. (4) 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. (2) Patients randomized to the treatment group received up to 3 courses of PDT separated by 90 days. The primary efficacy endpoint was the CR rate at any one of the endoscopic assessment timepoints. 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 CR compared to 38.6% in the control group. At the end of 24 months of follow-up, patients in the treatment group had an 83% chance of being cancer free compared to a 54% chance in the control group.

Five-year follow-up of subjects in the RCT of PDT with porfimer sodium (Photofrin) in Barrett’s high-grade dysplasia conducted for the FDA approval process was reported by Overholt et al. in 2007. (14) Patients with Barrett’s esophagus and high-grade dysplasia (HGD) were randomized to PDT plus omeprazole or omeprazole only. Sixty-one patients were enrolled in the long-term phase of the trial, 48 PDT plus omeprazole group and 13 in the omeprazole only group. Endoscopy with mucosal assessment and biopsies 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<0.0001). Patients in the PDT group were about half as likely to progress to cancer as those in the omeprazole alone group (21/138 [15%] vs. 20/70 [29%], respectively; p=0.027), with a significantly
longer time to progression to cancer favoring PDT. The small number of subjects available for long-term follow-up is a limitation of this study.

Badreddine and colleagues performed a retrospective analysis of a cohort of Barrett’s esophagus patients seen at a specialized Barrett’s esophagus clinic in the U.S. to identify risk factors for recurrence of dysplasia after ablative treatment including PDT. (15) 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 on the multivariate model were older age, presence of residual nondysplastic Barrett’s, and a history of smoking. The authors note that the possibility of missing prevalent dysplasia despite aggressive surveillance is a limitation in the study.

Pech and colleagues, in a study from Germany, report long-term (i.e., 5-year) outcomes of endoscopic treatment of high-grade intraepithelial neoplasia and mucosal adenocarcinoma in patients with Barrett’s esophagus. (16) Patients were excluded if staging examinations did not confirm the suspected diagnosis of Barrett’s carcinoma or high-grade intraepithelial neoplasia or if they showed more advanced tumor stage (greater than T1), lymph-node involvement, or metastasis. Patients with localized neoplasia were offered endoscopic resection; those with lesions that were not clearly localized, those with superficial subtle multifocal neoplasia, and patients with no neoplasia found in esophageal biopsies were treated with 5-aminolevulinic acid (5-ALA) PDT. (Note: Oral ALA does not have FDA approval.) Fifty-five patients received only PDT, and 13 had endoscopic resection and PDT. A complete response was achieved in 98.5% of the patients, and CR was achieved in 17% during median follow-up of 37 months.

Prasad et al. report similar outcomes between 2 groups (nonrandomized) of patients who received either PDT (n=129) or surgery (n=70) for high-grade dysplasia in Barrett’s esophagus. (17)

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. (18) 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’s 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=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 review of PDT for unresectable cholangiocarcinoma published in 2012 concluded that while data and experience with PDT are limited, PDT can be seen as a standard palliative therapy for unresectable cholangiocarcinoma. (19) Data to compare the efficacy of palliative PDT to other palliative therapy are absent.

Several case series have reported positive results, as measured by quality-of-life studies. (20-22) Two small randomized studies have reported both palliative effects and an increase in median survival. For example, Ortner and colleagues conducted a trial of 39 patients with nonresectable cholangiocarcinoma who were randomized to receive either endoscopic stenting alone or in conjunction with PDT. (23) The median survival of the 20 patients 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 and colleagues randomized 32 patients with cholangiocarcinoma to stenting with and without PDT. (24) The median survival for the PDT group was 21 months compared to 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. (25) 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.

Gao and colleagues performed a systematic review of the literature on PDT for unresectable cholangiocarcinoma. (26) The authors reviewed 2 RCTs, 2 comparative trials with concurrent controls, 1 comparative trial with historical controls, and 15 case series. The 2 randomized trials were rated of moderate quality, and the other available studies were of low to moderate quality. The mean number of subjects was 27 (range: 1–184 subjects). Porfimer sodium (Photofrin) was the photosensitizer used in all but 2 of the included studies. The RCTs were discussed above.

In a retrospective study by Kahaleh et al., 19 patients were treated with endoscopic retrograde cholangiopancreatography (ERCP) with PDT and stents, and 29 patients treated with ERCP and stents alone at a U.S. center. (27) Most of the patients had Bismuth III and IV lesions; however, some had Bismuth I and II lesions. Some patients in each group received chemoradiation therapy. Mortality in the PDT/stent group at 3, 6, and 12 months was 0%, 16%, and 56% respectively, and 28%, 52%, and 82% in the stent-alone group. The difference was statistically significant at 3 and 6 months. The authors' note 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 10-year period in Germany. (28) 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 patients 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. (29) On the negative side, he notes that PDT is not
available at all centers and requires expertise in endoscopy and PDT, and the 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. Post-treatment photosensitivity lasts for 4-6 weeks and may limit quality of life. In favor of PDT, it is reasonably well-tolerated, seems to be effective, and can be repeated without a ceiling dosage effect. It is the only treatment to date in which data suggest improved survival over plastic stent placement alone for advanced cholangiocarcinoma. Baron concludes 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.”

**Gynecological 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). (30) Thirty-two patients with recurrent gynecologic malignancies (9 cervical, 6 vulvar, 6 vaginal, 5 ovarian, 5 endometrial, and 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 received more than 1 treatment. Patients with vaginal and cervical recurrences also had moderate to severe burning sensation, with maximum treatment for 3 weeks.

**Endometrial Cancer**

In a retrospective Korean cohort study, Choi et al (2013) investigated the use of PDT as a fertility-sparing treatment for patients with early-stage (confined to the endometrium) endometrial cancer. (31) 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. (32) 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). (33) 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. (34) Patients with CIN grade 1 or 2 by local pathology review were randomized to 5% HAL, 1% HAL, 0.2% HAL, or placebo. Ointment and illumination (in active treatment groups) were applied by an indwelling device for 5 hours and 4.6 hours, respectively. The primary efficacy end point was patient response at 3 months, defined by regression of CIN and clearance of oncogenic HPV. After blinded central pathology review, 79% of randomized patients were confirmed as having CIN grade 1 or 2 and were included in efficacy analyses. Of these patients, 49% with CIN 1 and 83% with CIN 2 had oncogenic HPV infection. Statistically significant differences in CR at 3 months compared with placebo were observed only for patients with CIN 2 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. (35) 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. (36) 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. (37) 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. (38) 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). (39) Recurrence-free survival at 12, 24, and 30 months was 91%, 64%, and 60%, respectively.

Head and Neck Cancers

A systematic review published in 2013 reported on meta-tetra(hydroxyphenyl)chlorin (mTHPC) mediated PDT of squamous cell carcinoma in the head and neck. (40) Twelve studies met inclusion criteria for the review. Six reported on PDT with a curative intent and six on palliative treatment. Data from four of the 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 UW-QOL scale and the EORTC (QOL-C30/H&N-35).

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. (41) 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 (2013) (42) 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. (43) All patients had received radiation therapy and 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. (44) 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. (45) A novel photosensitizing agent (2-[1-hexyloxyethyl]-2-devinylpyropheorbide-a [HPPH]),
developed by the investigators, was used. At 48 months' 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. (46) 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).(47) 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 2007, 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. (48) 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. (49) 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. (50) Of 5 included studies, one was a series of 135 patients with reported CR in 76 cases (56%) and marked response in 47 cases (35%) 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.

**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 differences in survival outcomes.

Mesothelioma

PDT for treatment of mesothelioma has also been discussed in recent reviews; however, studies identified in the search consisted of Phase one studies and animal studies. A study from Austria with 14 subjects involved intraoperative PDT under hyperbaric oxygenation. (51) 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. (52) Intraoperative PDT had no statistically significant impact on survival.

Brain Cancer

At 2 university hospitals in Japan, Muragaki et al (2013) applied intraoperative PDT to 22 patients with newly diagnosed (n=21) or recurrent (n=1) primary malignant parenchymal brain tumors (approximately 50% glioblastoma). (53) 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 and others describe using intraoperative Photofrin PDT in 14 metastatic brain cancers (7 originating in the lung and 7 from a variety of sources). (54) Of the patients with lung cancer metastases, 1 died of unrelated cause, and 6 were free of brain disease until their deaths. 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. (55)

Prostate Cancer

PDT has been used for the management of prostate cancer. (56, 57) 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. (58) 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. Eymerit-Morin et al (2013) (59) reported on 56 patients who had participated in a randomized padeliporfin dose-finding trial. (60) 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. (61)

**Soft Tissue Sarcoma**

A 2013 retrospective, single-center study from Japan examined PDT in high-grade soft tissue sarcoma. (62) 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 overall survival (log-rank test, p=0.75) or 10-year local recurrence (p=0.36).

**Other Applications**

PDT has been used for the treatment of pancreatic cancer (63-64) and obstructive jaundice due to hepatocellular carcinoma (65) and oral premalignant lesions. (66) There is little evidence of PDT's efficacy for these indications.

**Ongoing Clinical Trials**

A search of online site ClinicalTrials.gov in February 2014 identified:

- 2 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).

- 2 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).

**Practice Guidelines and Position Statements**
American College of Chest Physicians
In 2013, the American College of Chest Physicians (ACCP) updated its evidence-based practice
guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of
the central airways. (67) ACCP recommends PDT and other endobronchial treatments (brachytherapy,
cryotherapy, electrocautery) "for patients with superficial limited mucosal lung cancer in the central
airway who are not candidates for surgical resection" (Grade 1C: strong recommendation based on
low-quality evidence). Guideline authors summarized the evidence for PDT in early lung cancer as
follows:

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

American Gastroenterological Association
The 2011 American Gastroenterological Association’s position statement on Barrett esophagus
management recommends photodynamic therapy as an option for treatment of confirmed HGD with
Barrett esophagus.(2)

European Association of Urology
European Association of Urology updated its guidelines on non-muscle-invasive bladder cancer in
2014.(68) PDT is not included as a treatment option.

National Comprehensive Cancer Network

Esophageal Cancer and Barrett Esophagus
The National Comprehensive Cancer Network (NCCN) guideline on esophageal cancer lists
photodynamic therapy as an ablative method for patients who have Barrett esophagus with HGD, and
for palliation of dysphagia in patients with esophageal cancer. Other treatment options for Barrett
NCCN esophagus with HGD include endoscopic mucosal resection (EMR) and ablation for T1a tumors,
and EMR or ablation for tumor in situ.

Cholangiocarcinoma
NCCN lists ablation (PDT is an ablative technique) as a treatment option for patients with microscopic
margins (R1) or residual local disease (R2) postresection of intrahepatic cholangiocarcinoma. NCCN
describes PDT as a relatively new therapy for local treatment of unresectable cholangiocarcinoma, stating that the combination of PDT and biliary stenting “has been shown to significantly improve the overall survival of patients with unresectable cholangiocarcinoma based on 2

Non-Small-Cell Lung Cancer
The NCCN guideline on non-small-cell lung cancer (NSCLC) states that PDT is a treatment option for patients with locoregional recurrence of NSCLC with endobronchial obstruction or severe hemoptysis. (71)

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

- Guidance for palliative treatment of advanced esophageal cancer, (72) treatment of localized inoperable endobronchial cancer, (73) and treatment of advanced bronchial carcinoma (74) state that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE guidance states that PDT should be used only with special arrangements for clinical governance, consent, and audit for the following 3 indications: interstitial photodynamic therapy for malignant parotid tumors, (75) early-stage esophageal cancer, (76) and bile duct cancer. (77)
- NICE guidance states that radiofrequency ablation or PDT may be considered for flat HGD, taking into account the evidence of their long-term efficacy, cost, and complication rates. (78)
- 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 RCTs with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality-of-life outcomes. (79)

**Society of Thoracic Surgeons**
The Society of Thoracic Surgeons published practice guidelines for the management of Barrett esophagus with HGD in June 2009. (80) 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.”

**U.S. Preventive Services Task Force Recommendations**
Not applicable.
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. Therefore, PDT may be considered medically necessary for palliative treatment of obstructing esophageal cancer and obstructing endobronchial lesions, treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy, treatment of high-grade dysplasia in Barrett’s esophagus and treatment of cholangiocarcinoma.

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. 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.

Medicare National Coverage

No National Coverage Determination

References


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<td>New Policy</td>
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<td>June 2013</td>
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<td>Policy updated with literature review through February 11, 2015; references 5, 10, 32-34, 64, 66, and 68 added; references 60 and 62 deleted. Policy statements unchanged.</td>
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Keywords

Hematoporphyrin
Oncologic Applications of Photodynamic Therapy
Photochemotherapy
Photodynamic Therapy
Photodynamic Therapy, Oncologic Applications
Photofrin®
Photoradiation Therapy
Photosensitizing Therapy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on File

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