8.01.06	Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus		
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Policy Statement

I. One or more courses of photodynamic therapy may be considered **medically necessary** for **any** of the following oncologic applications:
   A. Palliative treatment of obstructing esophageal cancer
   B. Palliative treatment of obstructing endobronchial lesions
   C. Treatment of early-stage non-small-cell lung cancer in individuals who are ineligible for surgery and radiotherapy
   D. Treatment of high-grade dysplasia in Barrett esophagus
   E. Palliative treatment of unresectable cholangiocarcinoma when used with stenting

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Focal therapy using photodynamic therapy for individuals with localized prostate cancer is addressed in Blue Shield of California Medical Policy: Focal Treatments for Prostate Cancer.

Coding
See the Codes table for details.

Description

Photodynamic therapy (PDT; also called phototherapy, photoradiotherapy, photosensitizing therapy, or photochemotherapy) is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance. Treatment for tumor cells occurs through selective retention of the photosensitizing agent and the selective delivery of light.

Related Policies

- Dermatologic Applications of Photodynamic Therapy
- Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus
- Focal Treatments for Prostate Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract

language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Labeled indications for porfimer sodium (Photofrin; Pinnacle Biologics), as approved by the U.S. Food and Drug Administration (FDA), are as follows.[1,]

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 neodymium-doped yttrium aluminum garnet laser therapy.

Endobronchial Cancer

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

High-Grade Dysplasia in Barrett Esophagus

- Treatment of high-grade dysplasia in Barrett esophagus patients who do not undergo esophagectomy.

As of May 2024 , oral 5-aminolevulinic acid has not received FDA approval as a photosensitizing agent for PDT. It is currently only indicated as an adjunct for the visualization of malignant tissue during surgery in individuals with glioma. Topical 5-aminolevulinic acid, used for the treatment of actinic keratoses, is addressed separately (Blue Shield of California Medical Policy: Dermatologic Applications of Photodynamic Therapy).

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

Rationale

Background

Photodynamic Therapy

Photodynamic therapy (PDT) has been investigated for use in a wide variety of tumors, including esophageal, lung, cholangiocarcinoma, prostate, bladder, breast, brain (administered intraoperatively), skin, and head and neck cancers. Barrett esophagus also has been treated with PDT. PDT for focal treatment of prostate cancer is discussed in Blue Shield of California Medical Policy: Focal Treatments for Prostate Cancer.

Several photosensitizing agents have been used in PDT: porfimer sodium (Photofrin®), administered intravenously 48 hours before light exposure, and 5-aminolevulinic acid, administered orally 4 to 6

hours before the procedure. Aminolevulinic acid is metabolized to protoporphyrin IX, which is preferentially taken up by the mucosa. Clearance of porfimer occurs in a variety of normal tissues over 40 to 72 hours, but tumor cells retain porfimer for a longer period. Laser treatment of Barrett esophagus may be enhanced by the use of balloons containing a cylindrical diffusing fiber. The balloon compresses the mucosal folds of the esophagus, thus increasing the likelihood that the entire Barrett mucosa is exposed to light. All patients who receive porfimer become photosensitive and must avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Obstructing Esophageal Cancer

Clinical Context and Therapy Purpose

The purpose of photodynamic therapy (PDT) as palliation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with obstructing esophageal cancer.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with obstructing esophageal cancer. Esophageal cancer is usually diagnosed at an advanced stage. A common clinical manifestation is dysphagia caused by obstruction of the esophagus by the tumor.

Interventions

The therapy being considered is PDT as palliation.
Photodynamic therapy (also called phototherapy, photoradiotherapy, photosensitizing therapy, or photochemotherapy) is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After

administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance.

Comparators
Comparators of interest include stenting, laser therapy, and argon plasma coagulation.

Outcomes
The general outcomes of interest are change in disease status, symptoms, quality of life, and treatment-related morbidity. Examples of relevant short-term outcomes are resolution of dysphagia and tumor response; the long-term outcome is disease-free survival. Note that long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting. Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival require longer follow-up.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Fayter et al (2010), on behalf of the National Institute for Health Research (NIHR), published a systematic review of 88 trials of PDT for the treatment of precancerous skin conditions, Barrett esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus, and skin.[2], Thirteen of these trials evaluated the use of PDT in patients with esophageal cancer: 5 focused on curative treatment and 8 focused on palliative treatments. Meta-analyses could not be conducted due to heterogeneity (patient characteristics, treatment protocols) among the trials. Reviewers could not draw any conclusions on PDT as a curative treatment, citing nonrandomization and nonblinding of assessors as limitations. There were limitations in the evidence for PDT as a palliative treatment, though some trials showed that outcomes with PDT were similar to the outcomes achieved with laser therapy. Results for the remaining indications are discussed in their respective sections.

A Cochrane review by Dai et al (2014)[3,] assessed treatments for dysphagia in esophageal cancer and identified 2 RCTs, both published in 1995,[4,5,] that compared laser treatment with PDT (N=278 patients), and 1 RCT of argon plasma coagulation (APC) alone, APC with PDT, or APC with high-dose-rate (HDR) brachytherapy (Rupinski et al [2011];[6,] discussed below). Results for laser versus PDT were driven by the larger trial (n=236). The risk of bias for the smaller RCT was rated as unclear while the risk of bias for the larger RCT was rated as low. In a meta-analysis, there was no statistical difference between treatments for improvement in dysphagia. The incidence of fever and photosensitivity were lower with laser treatment, and the incidence of perforation was lower with PDT. However, these estimates were imprecise.

McCann et al (2011) reported on a systematic review of traditional nonendoscopic and endoscopic treatments for early esophageal cancer, including 26 PDT studies.[7,] Reviewers noted the lack of evidence from large, randomized trials and found the overall quality of evidence low. Although evidence demonstrated reduced morbidity and mortality with endoscopic techniques compared with esophagectomy, outcomes across endoscopic treatments were similar, and no single endoscopic technique was identified as a recommended treatment approach. Reviewers focused on tumor

response and recurrence and disease-specific survival and overall survival (OS) and did not examine the quality of life outcomes.

Randomized Controlled Trials

Rupinski et al (2011), which was included in the 2014 Cochrane review summarized above, reported on a randomized trial of 93 patients with inoperable cancer of the esophagus or esophageal junction who were treated with APC alone, APC with PDT, or APC with HDR brachytherapy.[6,] Both combination therapies were more effective than APC alone in terms of median time to recurrence of dysphagia (85, 59, and 35 days for APC with HDR, APC with PDT, and APC alone, respectively). OS did not differ significantly between groups. Complications were more frequent in the APC with PDT and APC alone groups than in the APC with HDR group.

Section Summary: Obstructing Esophageal Cancer

At least 3 RCTs have compared various treatments including neodymium-doped yttrium aluminum garnet (Nd:YAG) laser or PDT plus APC with HDR brachytherapy plus APC or APC alone for dysphagia in esophageal cancer. A meta-analysis comparing PDT with Nd:YAG laser has suggested that improvements in dysphagia are similar, although estimates are imprecise. PDT is associated with a lower risk of perforation compared with a laser; however, PDT runs a high-risk of patients reacting adversely to light (e.g., photosensitivity). PDT plus APC appears to prolong time to recurrence of dysphagia compared with APC alone. The evidence is sufficient to determine that the use of PDT for palliation results in an improvement in the net health outcome.

Obstructing Endobronchial Tumors

Clinical Context and Therapy Purpose

The purpose of PDT in individuals who have obstructing endobronchial tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with obstructing endobronchial lesions.

Interventions

The therapy being considered is PDT as palliation.

Photodynamic therapy is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance.

Comparators

The following therapies are currently being used to make decisions about obstructing endobronchial lesions: laser therapy, brachytherapy, external-beam radiotherapy, and resection.

Outcomes

The general outcome of interest is symptom relief (dyspnea, cough, hemoptysis). Symptom relief and tumor response can be assessed over weeks to months.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
The porfimer sodium (Photofrin) prescribing information cites 2 studies with 211 patients with obstructing endobronchial tumors who were randomized to PDT or Nd:YAG laser therapy.[8,] Response rates (i.e., the sum of complete response and partial response rates) for the 2 treatments were similar at 1 week (59% PDT vs. 58% laser therapy), with a slight improvement at 6 weeks for PDT (60% PDT vs. 41% laser therapy). Clinical improvement, defined as improvements in dyspnea, cough, and hemoptysis, were similar for both groups at 1 week (25% to 29%); however, at 1 month and beyond, 40% of patients treated with PDT reported clinical improvement compared with 27% treated with laser therapy. Statistical comparisons were not performed due to missing data.

An RCT conducted by Akopov et al (2014) compared neoadjuvant chemotherapy with or without endobronchial PDT in 42 patients with non-small-cell lung cancer (NSCLC) initially considered inoperable due to bronchus/distal trachea involvement.[9,] The trial showed a greater proportion of patients who received PDT were able to undergo complete resection (pulmonectomy or lobectomy) compared with patients who did not receive PDT (89% vs. 54%; p=.002 [BCBSA calculation]). Diaz-Jimenez et al (1999), in a small, randomized study, compared PDT with Nd:YAG laser therapy for 31 patients who had airway obstruction.[10,] Efficacy over 24 months was similar. The incidence of immediate response was greater with laser therapy than with PDT, suggesting that laser therapy may be particularly appropriate for patients requiring rapid symptom relief.

Section Summary: Obstructing Endobronchial Tumors
At least 3 RCTs have compared PDT with a laser for symptom reductions in patients with obstructing endobronchial tumors. Patients generally reported similar symptom reductions with PDT and with a laser. Another RCT noted that adding PDT to neoadjuvant chemotherapy might increase the probability of undergoing complete surgical resection. The evidence is sufficient to determine that technology results in an improvement in the net health outcome.

Early-Stage Lung Cancer
Clinical Context and Therapy Purpose
The purpose of PDT in individuals who have early-stage lung cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with early-stage NSCLC who are not candidates for surgery or radiotherapy. Less than one-third of individuals with lung cancer present with early-stage disease. It is anticipated that relatively few individuals with non-obstructing lung cancer (who are not candidates for surgery) will be appropriate candidates for PDT. Of the 178,000 new cases of lung cancer annually, only 15% are detected with early-stage lung cancer. Of these, approximately 60% are treated with surgery, and another 25% are treated with radiotherapy.

Interventions
The treatment being considered is PDT, which is a 2 step procedure. First, a photosensitizing agent is injected into a vein to be absorbed by targeted tissues. Then optical fibers deliver light to the area, which activates the photosensitizing agents to ablate the targeted tissues. PDT can be used as a primary treatment or as an adjunctive treatment with surgery, radiotherapy, or chemotherapy.

Candidates for PDT are limited to those who cannot tolerate surgery or radiotherapy, most commonly due to underlying emphysema, other respiratory diseases, or prior radiotherapy.

Comparators

The following therapies are currently being used to make decisions about early-stage NSCLC who are not candidates for surgery or radiotherapy: radiofrequency ablation, cryotherapy, and brachytherapy.

Outcomes

The general outcomes of interest are tumor response rate and disease-free survival. Tumor response can be assessed within weeks to months. Assessment of response rates, recurrence, and disease-free survival requires longer follow-up.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

In the NIHR systematic review, Fayter et al (2010) identified several trials assessing PDT as a palliative treatment for late-stage lung cancer; however, no trials were identified on PDT for early-stage lung cancer.[2,] Evidence on PDT for early lung cancer consists of case series.

Case Series

The prescribing information for porfimer sodium (Photofrin) has described 3 case series of 62 patients with microinvasive lung cancer.[1,] Complete tumor response rate, biopsy-confirmed, at least 3 months after treatment was 50%; the median time to tumor recurrence exceeded 2.7 years; the median survival was 2.9 years; disease-specific survival was 4.1 years. In another case series, Kato et al (1996) evaluated 95 early-stage lung cancer patients treated with endoscopic PDT.[11,] The complete response rate was 83.2%. Table 1 summarizes the case series describing the use of porfimer sodium PDT for early-stage lung cancer.

Table 1. Photodynamic Therapy for Treatment of Early-Stage Non-Small Cell Lung Cancer

Study	Population	N	Results (95% CI)
FDA (Photofrin prescribing information) (2011)[1,]	Microinvasive, inoperable endobronchial tumors	62	• CR at 3 mo: 50% • Median survival: 2.9 y (2.1 to 5.7)
Endo et al (2009)[12,]	Centrally located early lung cancer; longitudinal tumor length ≤10 mm	48	• 5-y survival: 81% • CR:94%
Moghissi et al (2007)[13,]	Early central lung cancer, ineligible for surgery	21	• CR:100%
Corti et al (2007)[14,]	Early inoperable or recurrent NSCLC	40	• CR:72% • PR:20% • NR:6% • Median survival: 91 mo
Furukawa et al (2005)[15,]	Early-stage, central-type lung cancers	93	Lesion <1 cm: • CR:93%

Study	Population	N	Results (95% CI)
			• 5-y survival: 58% Lesion ≥1 cm: • CR:58% • 5-y survival: 59%
Kato et al (1996)[11,]	Early-stage, central-type lung cancers	95	CR:83%

CI: confidence interval; CR: complete response; FDA: U.S. Food and Drug Administration; NR: no response; NSCLC: non-small-cell lung cancer; PR: partial response.

The labeled indication for porfimer sodium suggests that PDT for early-stage lung cancer should be limited to those who are not candidates for surgery or radiotherapy. However, Cortese et al (1997) reported on a case series of 21 patients with early-stage squamous cell lung cancer who were offered PDT as an alternative to surgery.[16,] Patients were followed closely and underwent repeat endoscopy and/or surgical resection if cancer persisted after 1 or 2 courses of PDT. Nine (43%) patients had a complete response at a mean follow-up of 68 months (range, 24 to 116 months) and thus were spared surgical treatment.

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

Section Summary: Early-Stage Lung Cancer

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

Barrett Esophagus With High-Grade Dysplasia

Clinical Context and Therapy Purpose

The purpose of PDT in individuals who have Barrett esophagus with high-grade dysplasia (HGD) is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with Barrett esophagus with HGD.
Barrett esophagus is a condition in which the squamous epithelium that normally lines the esophagus is replaced by specialized columnar-type epithelium known as intestinal metaplasia in response to irritation and injury caused by gastroesophageal reflux disease. Barrett esophagus occurs in the distal esophagus; it may involve any length of the esophagus, it may be focal or circumferential, and it is visualized on endoscopy with a different color than background squamous mucosa. Confirmation of Barrett esophagus requires a biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and patients with Barrett esophagus are at a 40-fold increased risk for developing this disease compared to the general population. The rate of progression from low-grade dysplasia to either HGD or esophageal

adenocarcinoma ranges from 0.5% to 13.4% per patient per year.[17,] Once HGD is present, the risk of developing adenocarcinoma is 2% to 10% per patient per year; approximately 40% of individuals with HGD on biopsy are found to have associated carcinoma in the resection specimen.[2,] Management of Barrett esophagus includes endoscopic surveillance to detect the development of dysplasia or esophageal adenocarcinoma as early as possible to provide effective treatment. If low-grade dysplasia is detected, continued surveillance, radiofrequency ablation, or other endoscopic eradication therapies may be recommended. For patients with HGD, endoscopic eradication therapies are recommended, with the type of procedure dependent on patient age and life expectancy, comorbidities, the extent of dysplasia, local expertise in surgery and endoscopy, and individual preference.

Interventions

The treatment being considered is PDT, which is a 2 step procedure. First, a photosensitizing agent is injected into a vein to be absorbed by targeted tissues. Then optical fibers deliver light to the area, which activates the photosensitizing agents to ablate the targeted tissues. PDT can be used as a primary treatment or as an adjunctive treatment with surgery, radiotherapy, or chemotherapy.

Comparators

The following therapies are currently being used to make decisions about Barrett esophagus with HGD: radiofrequency ablation, surveillance, esophagectomy, and cryotherapy.

Outcomes

The general outcomes of interest are symptom relief, response rate, and progression to cancer. Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival require longer follow-up.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

The NIHR (2010) systematic review of PDT identified 11 RCTs evaluating PDT for Barrett esophagus, though only 4 focused on Barrett esophagus with HGD (the remaining had mixed HGD and low-grade dysplasia or no dysplasia).[2,] Reviewers concluded that PDT had beneficial effects on patients with Barrett esophagus with HGD, though studies had small sample sizes and were heterogeneous in comparators and PDT protocols.

A review of endotherapy for Barrett esophagus by Konda and Waxman (2012) indicated that, although studies have demonstrated long-term success with PDT for treating HGD in Barrett esophagus, its disadvantages have limited its continued use compared with newer modalities.[18,] Cited limitations of PDT included photosensitization, stricture formation, buried glands that harbor neoplastic potential, and decreased efficacy compared with new technologies.

Randomized Controlled Trials

The U.S. Food and Drug Administration (FDA) approved indication for treatment of HGD was based on a multicenter, partially blinded, study that randomized 199 patients to porfimer sodium (Photofrin) plus omeprazole or to omeprazole alone.[8,] Initially, 485 patients with HGD were screened for the trial;

49% were subsequently excluded because HGD was not confirmed on further evaluation. As noted in the prescribing information, the high patient exclusion rate reinforces the recommendation by the American College of Gastroenterology that the diagnosis of dysplasia in Barrett esophagus is confirmed by an expert gastrointestinal pathologist.[17,] Patients randomized to the treatment group received up to 3 courses of PDT 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 as ablation of all areas of HGD but some areas of low-grade dysplasia or Barrett epithelium may remain. Complete response was achieved by 76.8% of patients in the treatment group and 38.6% in the control group. After 24 months of follow-up, 13% of patients in the treatment group and 28% of patients in the control group had progressed to cancer.

Five-year follow-up of patients in the RCT previously described was reported by Overholt et al (2007).[19,] Sixty-one patients with Barrett esophagus and HGD were enrolled in the long-term phase of the trial; 48 were randomized to PDT plus omeprazole group, and 13 to omeprazole only. Endoscopy with mucosal assessment and biopsy was performed at the first visit and every 3 months thereafter until 4 consecutive quarterly biopsy results were negative for HGD and then biannually until 60 months after randomization or until treatment failure. At 5 years, PDT plus omeprazole (77% [106/138]) was significantly more effective than omeprazole alone (39% [27/70]; p<.001) in eliminating HGD. Patients in the PDT group (15% [21/138]) were approximately half as likely to progress to cancer as those in the omeprazole alone group (29% [20/70]; p=.027), with a significantly longer time to progression with PDT. Serious complications were reported by 12% of PDT patients versus 1% of omeprazole patients. Thirty-six percent of PDT patients developed strictures. The study was limited by the small number of patients available for long-term follow-up.

Dunn et al (2013) reported on an RCT that compared 5-aminolevulinic acid (5-ALA)-mediated PDT with porfimer sodium-mediated PDT for the treatment of 64 patients with Barrett esophagus with HGD.[20,] (Note: Oral 5-ALA does not have FDA approval as a photosensitizing agent for PDT.) Patients were recruited from a single university hospital in England. At 1 year, a complete reversal of dysplasia occurred in 16 (47%) of 34 patients randomized to 5-ALA and in 12 (40%) of 30 patients randomized to porfimer sodium (p=.62). With a 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 5-ALA group and 2 in the porfimer sodium group. Overall cancer incidence was 12% and 17% in the 5-ALA and porfimer sodium groups, respectively (p=.240). Strictures (26% vs. 7%) and photosensitivity (43% vs. 6%) were more common with porfimer sodium. Pleural effusions (7% vs. 18%) and transaminitis (0% vs. 47%) were more common with 5-ALA.

Kohoutova et al (2018) published a 5-year follow-up on 58 of the original 64 patients enrolled in the RCT reported by Dunn et al (2013).[21,] Of the 58 patients, 31 had been treated with 5-ALA PDT and 27 with porfimer sodium PDT. At median 67 months follow-up, no significant difference was found between the 5-ALA and porfimer sodium groups in a long-term complete reversal of intestinal metaplasia (78% vs. 63%, respectively; p=.18) and complete reversal of dysplasia (90% vs. 76%, respectively; p=.26). Thirteen 5-ALA patients (13/31; 42%) and 6 porfimer sodium patients (6/27; 22%) experienced no recurrence of dysplasia and received no further treatment. Many of the patients who required further treatment achieved long-term remission with endoscopic mucosal resection ± radiofrequency ablation (28 of 31 5-ALA patients and 10 of 16 porfimer sodium patients; p=.05). Investigators found that for 5-ALA alone, initial treatment success was a statistically significant predictor of long-term success (p=.03); however, the same was not true for porfimer sodium alone (p=.62). Kaplan-Meier analysis revealed that at 5-year follow-up the probability of developing invasive cancer was just below 20% for both groups who received multimodality treatment (p=.79). The study results suggest that neither 5-ALA nor porfimer sodium PDT are valuable long-term treatments for dysplastic Barrett esophagus.

Section Summary: Barrett Esophagus With High-Grade Dysplasia

For individuals with Barrett esophagus with HGD who receive PDT, the evidence includes 2 systematic reviews and 2 RCTs. One RCT compared PDT plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression, with cancer persisting during 5 years of follow-up for patients in the PDT plus proton inhibitor group. The results of the RCT also revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Another RCT compared PDT performed with different photosensitizers; results revealed that neither were valuable long-term treatments for dysplastic Barrett esophagus.

Unresectable Cholangiocarcinoma

Clinical Context and Therapy Purpose

The purpose of PDT in individuals who have unresectable cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with unresectable cholangiocarcinoma. Cholangiocarcinoma is rare, and the prognosis is generally poor due to the advanced stage at presentation. Individuals with unresectable cholangiocarcinoma typically decline rapidly with symptoms of biliary obstruction.

Interventions

The treatment being considered is PDT, which is a 2 step procedure. First, a photosensitizing agent is injected into a vein to be absorbed by targeted tissues. Then optical fibers deliver light to the area, which activates the photosensitizing agents to ablate the targeted tissues. PDT can be used as a primary treatment or as an adjunctive treatment with surgery, radiotherapy, or chemotherapy.

Comparators

The following therapy is currently being used to make decisions about unresectable cholangiocarcinoma: stenting alone.

Outcomes

The general outcomes of interest are improvements in quality of life and OS. Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival require longer follow-up. Note that long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Several systematic reviews (NIHR [2010],[2,] Gao et al [2010],[22,] Tomizawa and Tian [2012],[23,] Lu et al [2015],[24,]and Mohan et al [2022][25,]) have evaluated the use of PDT as an adjunct to stenting for the treatment of cholangiocarcinoma. The reviews identified 3 RCTs and several nonrandomized trials.

The 3 RCTs were considered good-to-moderate quality although the sample sizes were small (n=32, n=39, n=20). The nonrandomized studies were considered low-to-moderate quality. Porfimer sodium (Photofrin) was the photosensitizing agent used in all but 2 of the included studies. The most commonly reported adverse events were cholangitis (28%), phototoxicity (10%), and biloma (2%). One meta-analysis (Lu et al [2015][24,]) showed patients receiving PDT plus stenting experienced significantly longer OS (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.33 to 0.73; p<.01) than patients receiving stenting only. The 3 RCTs are discussed below. Another meta-analysis showed that the pooled survival rate with PDT was 11.9 months (95% CI, 10.7 to 13.1) compared to radiofrequency ablation (8.1 months; 95% CI, 6.4 to 9.9) and stent-only (6.7 months; 95% CI, 4.9 to 8.4).[25,]

Randomized Controlled Trials

Ortner et al (2003) conducted a trial of 39 patients with nonresectable cholangiocarcinoma who were randomized to endoscopic stenting alone or in conjunction with PDT.[26,] Median survival of the 20 patients in the PDT group was 493 days compared with 98 days in the 19 patients who underwent stenting alone. The trial was terminated prematurely due to these favorable results.

Zoepf et al (2005) randomized 32 patients with cholangiocarcinoma to stenting with and without PDT.[27,] Median survival was 21 months for the PDT group compared to 7 months in the control group. Hauge et al (2016) reported on the results of a phase 2, safety and feasibility RCT for combination chemotherapy plus stenting with and without temoporfin (Foscan) PDT in the treatment of biliary tract cancer.[28,] Eligible patients had unresectable or recurrent/metastatic biliary tract cancer, no previous chemotherapy or radiotherapy for current cancer, and no other cancers in the previous 5 years. Twenty patients were enrolled; 17 had hilar cholangiocarcinoma. In the PDT group, 1 PDT treatment was given following stenting and before chemotherapy. Chemotherapy was given until progression or for 12 courses. No serious, procedure-related adverse events were observed in either group. The number of grade 3 and 4 adverse events was similar in both groups. Three patients in each group developed cholangitis within 30 days. Following chemotherapy, mean quality of life as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 symptom score (range, 0 to 100) was 33 versus 24 for the fatigue domain, 14 versus 19 for the nausea and vomiting domain, and 14 versus 10 for the pain domain for PDT versus no PDT, respectively. Precision estimates were not given. Median progression-free survival was 139 days (range, 26 to 600 days) with PDT versus 96 days (range, 56 to 422 days) without PDT. Median OS was 238 days (range, 178 to 1,060) in the PDT group and 336 days (range, 110 to 690 days) in the no PDT group.

Observational Studies

Pereira et al (2012) reported on a prospective cohort study of 34 patients with unresectable cholangiocarcinoma who were treated with porfimer-mediated PDT at 3 centers in England.[29], Median survival was approximately 13 months with or without chemotherapy. At 5-year follow-up, all but 1 patient had died (5-year OS, 3%), mostly due to disease progression.

Several case series have reported positive quality of life outcomes with PDT.[30,31,32,] In an editorial, Baron (2008) reviewed the pros and cons of PDT for palliation of cholangiocarcinoma and the questions remaining about its role, given the available options of chemoradiation, brachytherapy, and plastic and metal stents.[33,] On the negative side, he noted that PDT is not available at all centers and requires expertise in both endoscopy and PDT; laser fibers available in the U.S. are suboptimal for endoscopic retrograde cholangiopancreatography use (because of their stiffness, treatment is limited to the main hepatic ducts); the procedure is time-consuming; and posttreatment photosensitivity lasts for 4 to 6 weeks, potentially limiting quality of life. In favor of PDT, the procedure is reasonably well-tolerated, seems to be effective, can be repeated without a ceiling dosage effect, and is the only treatment to date for which data suggest improved survival over plastic stent placement alone for advanced cholangiocarcinoma. Baron (2008) offered a "qualified yes" that PDT should be used for palliation of cholangiocarcinoma, but added that "further

comparative trials are needed to determine the optimal regimen of palliation of obstructive jaundice in these patients."

Section Summary: Unresectable Cholangiocarcinoma

Several observational studies and 3 small RCTs have found that PDT plus stenting is associated with greater elimination of bile duct stenosis and improved survival benefit compared with stenting alone. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival but not OS with similar rates of adverse events. Case series have suggested an improvement in the quality of life. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small number of cholangiocarcinoma patients, it is unlikely that stronger evidence will become available.

Other Malignancies

Clinical Context and Therapy Purpose

The purpose of PDT in individuals who have other malignancies such as gynecologic cancers, bladder cancer, head and neck cancers, brain cancer, soft tissue sarcoma (STS), and mesothelioma is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with gynecologic cancers, bladder cancer, head and neck cancers, brain cancer, STS, and mesothelioma.

Interventions

The treatment being considered is PDT, which is a 2 step procedure. First, a photosensitizing agent is injected into a vein to be absorbed by targeted tissues. Then optical fibers deliver light to the area, which activates the photosensitizing agents to ablate the targeted tissues. PDT can be used as a primary treatment or as an adjunctive treatment with surgery, radiotherapy, or chemotherapy.

Comparators

The following therapy is currently being used for other malignancies: standard of care, dependent on the type of malignancy.

Outcomes

The general outcomes of interest are: response rate, recurrence rate, and survival. Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival require longer follow-up.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Gynecologic Malignancies

Godoy et al (2013) reported on a retrospective cohort of women with recurrent gynecologic malignancies treated at a single United States center; 32 patients with recurrent gynecologic malignancies (9 cervical, 6 vulvar, 6 vaginal, 5 ovarian, 5 endometrial, 1 recurrent Paget disease of the anal canal) were treated with porfimer-mediated PDT.[34,] Five (24%) of 21 patients who had vaginal,

cervical, or anal recurrences achieved complete response (defined as a lack of detectable lesions within the area of treatment). The median time to response was 28 months. Some patients received more than one treatment. Patients with vaginal and cervical recurrences also had a 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.[35,] Sixteen patients were treated with PDT for grade 1 or 2 diseases (mean age, 31 years; range, 24 to 35 years). The photosensitizing agent was Photogem (non-FDA-approved) administered intravenously. The mean follow-up from diagnosis was 78 months (range, 8 to 140 months). After initial PDT, 12 (75%) of 16 patients showed complete response (defined as complete disappearance of adenocarcinoma or hyperplasia on follow-up dilation and curettage), and 4 patients were nonresponders. Four (33%) of the 12 initial responders experienced recurrence 6 months after complete response; 2 responded after additional PDT treatments. One of 4 initial nonresponders achieved a complete response after a second PDT treatment. Seven patients attempted to become pregnant, all initial responders. Four (57%) patients had 7 pregnancies, 4 with artificial reproductive technology and 3 by natural means, resulting in 6 live births. All births were by cesarean delivery. No evidence of endometrial cancer recurrence or hyperplasia was found before or after childbirth. In a similar study, Choi et al (2014) retrospectively reviewed 21 patients, 45 years of age and younger at diagnosis of early-stage (90% IA1 or IB1) cervical cancer who underwent a loop electrosurgical excision procedure or conization followed by PDT.[36,] This treatment was considered a fertility-preserving alternative to vaginal radical trachelectomy (excision of the uterine cervix). The median patient age was 31 years. At a mean follow-up of 53 months, 1 (5%) patient relapsed. Ten (77%) of 13 patients who attempted pregnancy were successful; live birth occurred in 7 cases, 5 of which were full-term deliveries.

Cervical Intraepithelial Neoplasia

Systematic Reviews

Zhang et al (2018) conducted a systematic review of PDT for cervical intraepithelial neoplasia (CIN) and human papillomavirus (HPV) infection.[37,] The literature search, conducted in May 2017, identified 4 RCTs comparing PDT (n=292) with placebo (n=141). The quality of the trials was considered very low. Meta-analyses found a significant increase in complete remission rate among patients with CIN (odds ratio [OR], 2.5; 95% CI, 1.2 to 5.1) and HPV infection (OR, 3.8; 95% CI, 1.9 to 7.7) receiving PDT compared with placebo. However, the adverse event rate was significantly higher for patients receiving PDT compared with patients receiving a placebo.

Tao et al (2014) in China published a systematic review of PDT for CIN.[38,] Literature was searched through March 2012, and 14 studies, mostly cohort studies and case series, were included (N=472 patients). Criteria for PDT efficacy varied across studies, but most (10/14) required biopsy. Overall, the complete response rate ranged from 0% to 100%. Two small RCTs (total n=60 patients) and 1 small case-control study (n=22) found no difference in complete response rate between PDT and placebo, PDT with hexylaminolevulinate (HAL) and PDT with methylaminolevulinate, or PDT and conization. Seven studies (n=319 patients) reported HPV eradication rates ranging from 53% to 80%.

Randomized Controlled Trials

Hillemanns et al (2015) reported on an international RCT of PDT with HAL in patients with CIN grades 1 or 2.[39,] 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 endpoint was the patient response at 3 months, defined by regression of CIN and clearance of oncogenic HPV. After a blinded central pathology review, 79% of randomized patients were confirmed as having CIN grade 1 or 2 and were included in efficacy analyses. Of these patients, 49% with CIN grade 1 and 83% with CIN grade 2 had an oncogenic HPV infection. Statistically significant differences in complete

response at 3 months compared with placebo were observed only for patients with CIN grade 2 who received 5% HAL (18 [95%] of 19 patients vs. 12 [57%] of 21 patients; p=.009). All responders in both groups maintained a response 6 months after the last treatment. Five (2%) of 262 randomized women became pregnant within 3 months of the last treatment, and all delivered healthy full-term infants. Interpretation of these results was limited by the lack of randomization among patients included in efficacy analyses and the lack of statistical correction for multiple testing.

Case Series

In a study included in the Tao et al (2014) 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.[40,] Complete regression of neoplastic lesions was seen in 104 (93%) 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 vaginal and 2 by cesarean delivery.

Subsequent to the literature search of the Tao et al (2014) 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.[41,] Patients were randomized to 1 of 6 treatment groups defined by varying dosages of the photosensitizing agent, HAL, or methylaminolevulinate (neither FDA-approved for systemic use). The primary endpoint was a complete response at 6 months, defined as normal histology and cytology. Women treated with HAL 40 mM applied twice in 3 hours (vs. 12 hours) followed by a light dose of 50 to 100 J/cm^3 had the best response (83% among women with CIN grade 2). Groups were not powered for statistical comparison.

Vulvar Intraepithelial Neoplasia

Winters et al (2008) reported on a phase 2 European study of imiquimod and PDT for vulvar intraepithelial neoplasia in 20 patients.[42,] At baseline, 95% of patients were symptomatic; at 52 weeks, 65% of patients were asymptomatic. A more recent review of the literature of PDT for vulvar intraepithelial neoplasia identified 8 case series that found PDT to be an effective treatment for vulvar intraepithelial neoplasia, but there was heterogeneity among the studies in type and dose of PDT and follow up ranged widely from 6 weeks to 2 years.[43,]

Bladder Cancer

Investigators in Germany and Korea have examined cohorts with non-muscle-invasive bladder cancer treated with PDT after transurethral resection of the bladder. Bader et al (2013) applied intravesical hexaminolevulinate (Hexvix) and bladder wall irradiation to 17 patients with intermediate- or high-risk urothelial cell carcinoma.[44,] Six-, 9-, and 21-month disease-free survival rates were 53%, 24%, and 12%, respectively. Lee et al (2013) applied intravenous Radachlorin (non-FDA-approved) and bladder wall irradiation to 34 patients with high-grade urothelial cell carcinoma refractory or intolerant to bacillus Calmette-Guérin therapy (for recurrence prevention).[45,] Recurrence -free survival rates at 12, 24, and 30 months were 91%, 64%, and 60%, respectively.

Head and Neck Cancers

Systematic Reviews

Gondivkar et al (2017) published a systematic review of PDT for the management of potentially malignant oral disorders and head and neck squamous cell carcinoma.[46,] Twenty-six studies (N=988 patients; range, 2 to 147 patients) of several different photosensitizers were included (5-ALA, meta-tetrahydroxyphenylchlorin [Foscan], hematoporphyrin derivatives, Photofrin, Photosan, and chlorin e6). All studies were prospective; only 1 study was comparative. In studies reporting response rates, complete, partial, and no response rates to PDT ranged from 23% to 100%, 4% to 66%, and 0% to 39%, respectively, for potentially oral malignant disorders, and complete response rates ranged from 16% to 100% for head and neck carcinoma. The recurrence rate for potentially malignant oral disorders ranged from 0% to 36% in 12 studies.

In a systematic review from The Netherlands, de Vissche et al (2013) reported on meta-tetrahydroxyphenylchlorin (Foscan; non-FDA-approved)-mediated PDT for squamous cell carcinoma of the head and neck.[47,] Twelve studies met inclusion criteria: 6 reported on PDT with curative intent and 6 as palliative treatment. Data from 4 studies reporting on curative therapy were pooled (n=301 patients). Reviewers concluded that data were insufficient to permit conclusions on PDT for curative intent. Palliative therapy appeared to improve quality of life by approximately 30% at 4 months for those with head and neck cancer, as measured by the University of Washington Quality of Life Questionnaire and the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer.

The NIHR systematic review (2010) identified 4 studies (N=276) evaluating PDT for the treatment of head and neck cancer.[2,] One trial was a full publication and 3 were abstracts. All were considered poor quality. The single RCT included patients with nasopharyngeal cancer (n=30) and suggested that the use of PDT to treat nasopharyngeal cancer merited additional investigation.

Wildeman et al (2009) reviewed evidence on the efficacy of PDT in patients with recurrent nasopharyngeal carcinoma.[48,] Of 5 studies included, 1 was a series of 135 patients, which reported a complete response in 76 (56%) patients and a marked response in 47 (35%) patients after hematoporphyrin derivative-mediated PDT; however, it was unclear whether PDT was first- or subsequent-line treatment. The other 4 studies had 12 or fewer subjects.

Comparative Studies

At a single center in The Netherlands, Karakullukcu et al (2013) conducted a retrospective, matched cohort study of 98 patients with primary T1/T2N0M0 squamous cell carcinoma of the oral cavity to a maximum depth of 5 mm.[49,] The study compared meta-tetrahydroxyphenylchlorin-mediated PDT with surgery. Fifty-five patients received PDT, and a cohort of 43 patients matched by age, sex, presentation (primary or secondary), and tumor location, depth, and stage underwent transoral surgery. There were no statistical differences between groups in 5-year disease-free survival (47% with PDT vs. 53% with surgery; Cox proportional hazard, p=.75), 5-year local recurrence-free survival (67% vs. 74%; p=.13), or OS (83% vs. 75%; p=.17).

Noncomparative Studies

Ahn et al (2016) reported on the outcomes of a phase 1 study of PTD with 5-ALA for premalignant and early-stage head and neck tumors.[50,] Thirty-five patients were enrolled and 30 received PDT ranging from 50 to 200 J/cm^2. The median follow-up was 42 months. The most common toxicity was grade 3 mucositis (52%). One patient developed grade 5 sepsis and died, which might have been related to treatment. The complete response rate at 3 months was 69%. Including all follow-up, 34% of patients developed local recurrence and 34% developed recurrence adjacent to the treated field.

Biel (2007) reported on 276 patients treated with PDT with Photofrin for early oral and laryngeal cancers over nearly 16 years.[51,] Of 115 patients in this case series who had recurrent or primary carcinoma in situ, T1N0, and T2N0, the 5-year cure rate was 100%; at a mean follow-up of 91 months, 10 recurrences were reported. For 113 patients with recurrent or primary carcinoma in situ and T1N0 squamous cell carcinoma of the oral cavity, there were 6 recurrences within 8 months of initial treatment salvaged with either repeat PDT or surgical resection. Two patients with T1 tongue tumors developed positive regional lymph nodes within 3 months of PDT, had conventional neck dissection, and were disease-free for at least 5 years. In 48 patients treated for superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity, there were 5 recurrences, all salvaged with repeat PDT or surgical resection. The 3-year cure rate was 100% (mean follow-up, 56 months).

Numerous small (sample size range, 7 to 30 patients), uncontrolled studies have been reported on PDT for laryngeal, oral, and nasopharyngeal cancers.[52,53,54,55,56,57,58,] Different outcomes were reported across studies. Of the studies reporting response rates, complete response was observed in 67% to

100% of patients treated with PDT. Three studies collected data on OS. One of them reported a 4-year OS rate of 67%[55,] The others reported a 5-year OS rate of 36% [54,]and 24%, respectively.[58,]

Brain Cancer

The NIHR systematic review (2010) identified 2 trials using PDT to treat brain cancer.[2,] One trial was considered to be poor quality and therefore did not provide useful evidence. The other trial, an RCT (n=27), compared standard resection with standard resection plus repetitive 5-ALA PDT to treat patients with glioblastoma multiforme. Patients receiving the resection plus PDT experienced significantly longer survival (52.8 vs. 24.2 weeks) and significantly longer time to recurrence (8.6 vs. 4.8 months) compared with patients receiving surgery alone.

At 2 university hospitals in Japan, Muragaki et al (2013) applied intraoperative PDT to 22 patients with newly diagnosed (n=21) or recurrent (n=1) primary malignant parenchymal brain tumors (50% glioblastoma).[59,] The photosensitizing agent was talaporfin sodium (Laserphyrin; non-FDA-approved). At 6 months, 2 patients had local progression (6-month progression-free survival, 91%); at 1 year, 1 patient had died (1-year OS, 95.5%). Median progression-free survival was 20 months (95% CI, 10.3 to not estimated), and median OS was 27.9 months (95% CI, 24.8 to not estimated).
Aziz et al (2009) used intraoperative PDT with Photofrin in 14 patients with metastatic brain cancer (7 originating in the lung, 7 from a variety of sources).[60,] Of the patients with lung cancer metastases, 1 died of an unrelated cause, and 6 were free of brain disease until death. Two of the remaining patients (1 with metastatic bowel cancer, 1 with unknown primary) died of local brain recurrence.

Soft Tissue Sarcoma

Nakamura et al (2018) investigated the long-term clinical efficacy of acridine orange (AO, a non-FDA-approved fluorescent dye) therapy combined with photodynamic surgery, PDT, and radiodynamic therapy on the inhibition of local recurrence after marginal intra-lesion tumor resection in high-grade STSs.[61,] In this pilot study, the investigators evaluated a total of 48 patients who had received AO therapy that used different combinations of photodynamic surgery, PDT, and radiodynamic therapy after marginal or intralesional resection for high-grade STSs (Fédération Nationale des Centres de Lutte Contre le Cancer[62,] grade 2 or 3) between 1999 and 2014. Local recurrence-free rates at 5 years and 10 years post-procedure were 78.9% and 73.3%, respectively. Multivariate analysis revealed that patients with larger tumors had significantly poorer local control (HR, 1.2; 95% CI, 1.068 to 1.349; p=.002). Women had significantly better local control (HR, 0.212; 95% CI, 0.045 to 0.986; p=.048). Patient age, the status of primary tumors (primary vs local recurrence), administration of chemotherapy, Fédération Nationale des Centres de Lutte Contre le Cancer grade, and type of AO therapy administered did not significantly predict local control. Data provided by this study did not assess the role PDT alone played in patient outcomes. The study is not an RCT and included a small number of patients, which limits the generalizability of the results. The investigators conclude that, although further studies are needed, AO therapy may be beneficial for long-term local control of high-grade STSs; however, tumor size should be considered.

In a retrospective, single-center study from Japan, Matsubara et al (2013) examined PDT in high-grade soft tissue sarcoma.[63,] AO was used as the photosensitizer in 51 PDT-treated patients. Compared with 119 patients who underwent conventional wide-margin resection for limb salvage surgery, there was no statistical difference in 10-year OS (p=.75) or 10-year local recurrence (p=.36).

Mesothelioma

In a study from Austria, Matzi et al (2004) compared decortication alone (n=11) with decortication plus PDT under hyperbaric oxygenation (n=14) in patients with advanced malignant mesothelioma.[64,] The authors concluded that the addition of PDT was safe and technically feasible in the palliative setting. 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.[65,] Intraoperative PDT had no statistically significant impact on survival.

Friedberg et al (2017) presented a retrospective case series of 73 patients with malignant pleural mesothelioma undergoing lung-sparing surgery and PDT.[66,] Median follow-up was 5.3 years, with a median OS of 3 years and disease-free survival of 1.2 years. The retrospective nature of the study and the significant variability in chemotherapy administration among the patients limits the interpretation of the results.

Other Applications

PDT has been used for the treatment of pancreatic cancer,[67,68,] obstructive jaundice due to hepatocellular carcinoma,[69,] and oral premalignant lesions.[70,] There is little evidence of PDT's efficacy for these indications.

Section Summary: Other Malignancies

The evidence for PDT to treat gynecologic malignancies includes several RCTs enrolling patients with cervical cancer, while the remaining studies on other gynecologic malignancies are mostly uncontrolled and observational. Efficacy results were inconsistent, with the complete response for PDT in cervical cancer ranging from 0% to 100%. Four RCTs have compared PDT with placebo for CIN. A meta-analysis found significant improvements in complete response rate with PDT, however, the trials were considered low quality and adverse events rates were significantly higher with PDT. The evidence for PDT to treat bladder cancer consists of 2 small cohort studies, using non-FDA-approved photosensitizers. Small sample sizes and the lack of comparators limit the interpretation of results.

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

The evidence for PDT to treat brain cancer consists of 1 RCT and a case series. The RCT reported significantly longer survival and time to recurrence in the PDT group compared with the surgery-alone group. The small sample size of this RCT and the lack of comparators in the other studies limit the interpretation of results.

The evidence for PDT to treat STS consists of a retrospective study that reported no difference in OS or recurrence in patients undergoing surgery with or without PDT.

The evidence for PDT to treat mesothelioma consists mostly of nonrandomized small studies. One larger retrospective study reported significantly longer survival and time to recurrence in the PDT group than in the surgery alone group, but the retrospective nature of the study and the significant variability in chemotherapy administration among the patients limits the interpretation of the results. The evidence for PDT to treat pancreatic cancer, hepatocellular carcinoma, and oral lesions is not sufficiently robust to draw conclusions about efficacy.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians

In 2013, the American College of Chest Physicians updated its evidence-based guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways.[71,] The College recommended photodynamic therapy (PDT) and other endobronchial treatments (brachytherapy, cryotherapy, electrocautery) "for patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection" (grade 1C: strong recommendation based on low-quality evidence). The guidelines summarized the evidence for PDT in early lung cancer as follows:

- "PDT appears to be an effective therapeutic modality for small early-stage centrally located lung cancers, the majority of which are SqCCs [squamous cell carcinomas]. CR [complete response] 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. NPe6 [talaporfin sodium], a newer-generation photosensitizer, appears to be as effective but better tolerated than older agents. However, these data have only been reported by 1 group and need to be validated in larger numbers of patients."

American College of Gastroenterology

In 2016, the American College of Gastroenterology guidelines on diagnosis and management of Barrett esophagus stated that there is level I evidence for prevention of cancer for PDT and radiofrequency ablation in Barrett esophagus with high-grade dysplasia (HGD).[72,] The guidelines also stated: "Given the costs and side-effect profile of photodynamic therapy, as well as the large body of data supporting the safety and efficacy of radiofrequency ablation, this modality appears to be the preferred therapy for most patients." The 2021 updated guidelines make the following recommendation related to endoscopic therapy: "We suggest endoscopic therapy in patients with BE [Barrett esophagus] confirmed with LGD [low-grade dysplasia] to reduce the risk of progression to HGD/EAC [esophageal adenocarcinoma], with endoscopic surveillance of confirmed LGD as an acceptable alternative (strength of recommendation: conditional; quality of evidence: moderate)."[73,] However, the guideline does not specifically mention PDT and only mentions radiofrequency ablation in the context of endoscopic therapy.

American Gastroenterological Association

In 2011, the American Gastroenterological Association's (AGA) position statement on Barrett esophagus management recommended PDT as an option for the treatment of confirmed HGD with Barrett esophagus.[17,] In 2020, the AGA published a clinical practice update on the endoscopic treatment of Barrett esophagus with dysplasia and/or early cancer.[74,] The practice update provides a best practice statement that states that endoscopic therapy, which may include ablative therapies such as PDT, is the preferred treatment for Barret esophagus with HGD. In 2021, AGA released an expert review clinical practice update on the optimal management of malignant alimentary tract obstruction.[75,] It stated that "For patients who present with esophageal obstruction from esophageal cancer who are not candidates for resection, clinicians should consider either SEMS [self-expanding metal stent] insertion or brachytherapy as sole therapy or in combination. Clinicians should not consider the use of laser therapy or photodynamic therapy because of the lack of evidence of better outcomes and superior alternatives."

National Comprehensive Cancer Network

Esophageal Cancer and Barrett Esophagus

The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2024) for esophageal cancer state that radiofrequency ablation has become the preferred treatment while PDT is an alternative strategy for patients who have Barrett esophagus with HGD.[76,]Regarding palliative PDT, they note that "long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG [neodymium-doped yttrium aluminum garnet] laser, PDT, and cryoablation, or endoscopic and radiographic-assisted insertion of expandable metal or plastic stents." The guidelines also state that

PDT can effectively treat esophageal obstruction but "is less commonly performed due to photosensitivity and costs" compared with radiotherapy and brachytherapy.

Cholangiocarcinoma

The NCCN (v.2.2024) guidelines on biliary tract cancers describe PDT as a relatively new therapy for local treatment of unresectable cholangiocarcinoma, stating that the combination of PDT and biliary stenting "was reported to be associated with prolonged overall survival in patients with unresectable cholangiocarcinoma based on 2 small randomized clinical trials [Ortner et al (2003)[26,] and Zoepf et al (2005)[27,]."[77,]".

Non-Small-Cell Lung Cancer

The NCCN guidelines (v.5.2024) on non-small-cell lung cancer state that PDT is a treatment option for patients with locoregional recurrence of non-small-cell lung cancer with an endobronchial obstruction or severe hemoptysis.[78,]

National Institute for Health and Care Excellence

The NICE has published guidance on a number of applications of PDT.

- Guidance for palliative treatment of advanced esophageal cancer,[79,] treatment of localized inoperable endobronchial cancer,[80,] and treatment of advanced bronchial carcinoma[81,] has indicated that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE guidance has indicated that PDT should not be used for the following 3 indications due to poor quality evidence: interstitial photodynamic therapy for malignant parotid tumors,[82,] early-stage esophageal cancer,[83,] and bile duct cancer.[79,]
- NICE guidance has indicated that PDT may be considered for Barrett esophagus with flat HGD, taking into account the evidence of their long-term efficacy, cost, and complication rates.[84,] The guidance notes that current evidence on the use of PDT for Barrett esophagus with either low-grade dysplasia or no dysplasia is inadequate so that the balance of risk and benefit is unclear.
- NICE guidance on PDT for brain tumors has indicated that current evidence is limited in quality and quantity, and the procedure should only be used in the context of randomized controlled trials with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality of life outcomes.[85,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02153229	A Randomized Phase 2 Trial of Radical Pleurectomy and Post-Operative Chemotherapy With or Without Intraoperative Porfimer Sodium -Mediated Photodynamic Therapy for Patients With Epitheliod Malignant Pleural Mesothelioma	102	Dec 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04860154	Evaluation of Bile Duct Patency After Photodynamic Therapy in Unresectable Cholangiocarcinoma: a Prospective Non-randomized Controlled Study	200	May 2024
Unpublished			
NCT00587600	Biomarkers in Phototherapy of Barrett's Esophagus	208	Apr 2017

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for photodynamic therapy, including type and location of cancer and reason why surgery cannot or should not be used if applicable
  - Documentation of curative intent
  - Previous treatments and response

Post Service (in addition to the above, please include the following):

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (e.g., laser therapy, cryotherapy)
	43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
	96570	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
	96571	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
HCPCS	C9738	Adjunctive blue light cystoscopy with fluorescent imaging agent (list separately in addition to code for primary procedure)
	J9600	Injection, porfimer sodium, 75 mg

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2010	New policy Combined the following BSC policies:

Effective Date	Action
	• Photodynamic Therapy (PDT) for Esophageal and Lung Cancers • Photodynamic Therapy (PDT) for High Grade Esophageal Dysplasia
06/30/2015	Policy title change from Photodynamic Therapy for Cancer Policy revision without position change
05/01/2017	Policy revision without position change
10/01/2017	Policy revision without position change
03/01/2018	Coding update
09/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement. Literature review updated.
09/01/2021	Annual review. No change to policy statement. Literature review updated.
09/01/2022	Annual review. Policy statement and literature review updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.
09/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus 8.01.06 **Policy Statement:** I. One or more courses of photodynamic therapy may be considered **medically necessary** for **any** of the following oncologic applications: A. Palliative treatment of obstructing esophageal cancer B. Palliative treatment of obstructing endobronchial lesions C. Treatment of early-stage non-small-cell lung cancer in individuals who are ineligible for surgery and radiotherapy D. Treatment of high-grade dysplasia in Barrett esophagus E. Palliative treatment of unresectable cholangiocarcinoma when used with stenting II. Other oncologic applications of photodynamic therapy are considered **investigational** including, but not limited to, other malignancies and Barrett esophagus without associated high-grade dysplasia.	**Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus 8.01.06** **Policy Statement:** I. One or more courses of photodynamic therapy may be considered **medically necessary** for **any** of the following oncologic applications: A. Palliative treatment of obstructing esophageal cancer B. Palliative treatment of obstructing endobronchial lesions C. Treatment of early-stage non-small-cell lung cancer in individuals who are ineligible for surgery and radiotherapy D. Treatment of high-grade dysplasia in Barrett esophagus E. Palliative treatment of unresectable cholangiocarcinoma when used with stenting II. Other oncologic applications of photodynamic therapy are considered **investigational** including, but not limited to, other malignancies and Barrett esophagus without associated high-grade dysplasia.