

**Medical Policy**

**MP 8.01.06**  
Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

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**POLICY**

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 radiotherapy
- treatment of high-grade dysplasia in Barrett esophagus
- palliative treatment of unresectable cholangiocarcinoma when used with stenting

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

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**POLICY GUIDELINES**

Focal therapy using photodynamic therapy for individuals with localized prostate cancer is addressed in policy 8.01.61.

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**CODING**

The following CPT codes may be used to describe endoscopic photodynamic therapy:

- 96570 Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drugs; first 30 minutes. (List separately in addition to code for endoscopy or bronchoscopy)
- 96571 as above, but each additional 15 minutes.

As noted in the CPT code description, the procedure will be coded in conjunction with an endoscopy or bronchoscopy.
bronchoscop y, which may be coded as follows:

43229 Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesions (includes pre- and post-dilation and guide wire passage, when performed)
31641 Bronchoscopy, rigid or flexible, including fluoroscopic guidance when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy).

Claims also may be identified by the use of HCPCS code J9600, describing the drug, porfimer sodium.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES
State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

OBSTRUCTING TUMORS
Esophageal cancer is usually diagnosed at an advanced stage. A common clinical manifestation is dysphagia caused by obstruction of the esophagus by the tumor.

Lung cancer is a common cause of airway obstruction that can manifest as dyspnea, coughing, and wheezing. The intervention used to manage obstruction depends on several factors, including etiology and acuteness.

Treatment
There are several nonsurgical approaches to provide palliation of dysphagia including photodynamic therapy (PDT). For patients without life-threatening airway obstruction, PDT is an option for providing palliative relief of symptoms.

EARLY-STAGE LUNG CANCER
Less than one-third of lung cancer patients present with early-stage disease. It is anticipated that relatively few patients with nonobstructing 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. Candidates for PDT are limited to those patients who cannot tolerate surgery or radiotherapy, most commonly due to underlying emphysema, other respiratory disease, or prior radiotherapy.

Treatment
For patients with early-stage disease, surgery is the standard treatment. For inoperable early non-small-cell lung cancer (v.4.2018), treatment guidelines from the National Comprehensive Cancer Network recommend stereotactic ablative radiotherapy.¹ The guidelines reference a phase 2 multicenter noncomparative trial of stereotactic body radiotherapy by Baumann et al (2009) who assessed 57 patients with inoperable stage I non-small-cell lung cancer, the results of which demonstrated a 3-year overall survival of 88%.² For patients who are not surgical candidates or who refuse surgery and are ineligible for radiotherapy, other ablative techniques (eg, PDT) are options.
**BARRETT ESOPHAGUS**

The esophagus is normally lined by squamous epithelium. Barrett esophagus is a condition in which 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. 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 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 with the general population. Esophageal adenocarcinoma is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, resulting in histologic phenotypic expression ranging from low-grade dysplasia to high-grade dysplasia (HGD) to carcinoma. Most patients with nondysplastic Barrett esophagus do not progress beyond nondysplasia; the estimated rate of progression is 0.9% per patient per year. By comparison, the rate of progression from low-grade dysplasia to either HGD or esophageal adenocarcinoma ranges from 0.5% to 13.4% per patient per year. Once HGD is present, the risk of developing adenocarcinoma is 2% to 10% per patient per year; approximately 40% of patients with HGD on biopsy are found to have associated carcinoma in the resection specimen.

**Treatment**

Management of Barrett esophagus includes endoscopic surveillance, in order 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 patient preference.

**CHOLANGIOCARCINOMA**

Cholangiocarcinoma is rare and the prognosis is generally poor due to the advanced stage at presentation. Patients with unresectable cholangiocarcinoma typically decline rapidly with symptoms of biliary obstruction.

**Treatment**

Several palliative therapies have been suggested, including PDT, to reduce symptoms and improve quality of life.

**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 evidence review 8.01.61.

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.

REGULATORY STATUS
Labeled indications for porfimer sodium (Photofrin®; Pinnacle Biologics), as approved by the U.S. Food and Drug Administration through a new drug application in 2011, are as follows.5

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.
- Treatment of microinvasive endobronchial non-small-cell lung cancer in patients for whom surgery and radiotherapy are not indicated.

HGD in Barrett Esophagus
- Treatment of HGD in Barrett esophagus patients who do not undergo esophagectomy.

As of June 2018, oral 5-aminolevulinic acid has not received Food and Drug Administration approval as a photosensitizing agent for PDT. Topical 5-aminolevulinic acid, used for the treatment of actinic keratoses, is addressed separately (evidence review 2.01.44).

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 phopheresis, which involves withdrawing blood from the patient, irradiating it with ultraviolet light, and then returning the blood to the patient. Extracorporeal phopheresis is addressed separately.

RATIONALE
This evidence review was created in December 1995 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 7, 2018. Most studies from outside the United States use photosensitizing agents that have not been cleared for use in the United States.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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.

**OBSTRUCTING ESOPHAGEAL TUMORS**

**Clinical Context and Test Purpose**
The purpose of photodynamic therapy (PDT) in patients who have obstructing esophageal tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with obstructing esophageal tumors?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients with obstructing esophageal cancer.

**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 obstructing esophageal cancer: stenting, laser therapy, and argon plasma coagulation.

**Outcomes**
The general outcomes of interest are as follow: the short-term outcome is the 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.

**Timing**
Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival requires longer follow-up.

**Setting**
PDT is administered in a tertiary care setting.

**Systematic Reviews**
Fayter et al (2010), on behalf of the National Institute for Health Research (NIHR), published a systematic review of PDT for the treatment of precancerous skin conditions, Barrett esophagus, and cancers of the biliary tract, brain, head and neck, lung, esophagus, and skin. Reviewers selected literature published through June 2009 and included 88 trials. 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 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), who assessed treatments for dysphagia in esophageal cancer, identified two 1995 RCTs that compared laser treatment with PDT (total N=278 patients) and an RCT of argon plasma coagulation (APC) alone, APC with PDT, or APC with high-dose rate (HDR) brachytherapy (Rupinski et al [2011], discussed below). Results for laser vs 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 because of very wide confidence intervals (CIs).

McCann et al (2011) reported on a systematic review of traditional nonendoscopic and endoscopic treatments for early esophageal cancer, including 26 PDT studies. Reviewers noted the lack of evidence from large, randomized trials and found the overall quality of evidence low. Although evidence demonstrated reduced morbidity and mortality with endoscopic techniques compared with esophagectomy, outcomes across endoscopic treatments were similar, and no single endoscopic technique was identified as a recommended treatment approach. Reviewers focused on tumor response and recurrence and disease-specific survival and overall survival (OS) and did not examine 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. 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 plus PDT and APC alone groups than in the APC with HDR group.

Nonrandomized Studies
The prescribing information for porfimer sodium (Photofrin) describes a multicenter, single-arm study of PDT in 17 patients with obstructing esophageal cancer reported by Li et al (2010). Patients received from 1 to 3 monthly treatments. Of 17 treated patients, 11 (65%) received clinically important benefit from PDT (defined as complete tumor response, normal swallowing, or improvement in dysphagia). After PDT, endoscopic débridement of the esophagus may be required, and the residual tumor can be retreated during this process.

Section Summary: Obstructing Esophageal Tumors
At least 3 RCTs have compared various treatments including Nd:YAG laser or PDT plus APC with HDR brachytherapy plus APC or APC alone for dysphagia in esophageal cancer. 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 (eg, photosensitivity). PDT plus APC appears to prolong time to recurrence of dysphagia compared with APC alone.
OBSTRUCTING ENDOBRONCHIAL TUMORS

Clinical Context and Test Purpose
The purpose of PDT in patients who have obstructing endobronchial tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with obstructing endobronchial tumors?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients with obstructing endobronchial lesions.

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 obstructing endobronchial lesions: laser therapy, brachytherapy, external-beam radiotherapy, and resection.

Outcomes
The general outcome of interest is symptom relief (dyspnea, cough, hemoptysis).

Timing
Symptom relief and tumor response can be assessed over weeks to months.

Setting
PDT is administered in a tertiary care setting.

Randomized Controlled Trials
The Photofrin prescribing information cites 2 studies with 211 patients with obstructing endobronchial tumors who were randomized to PDT or Nd:YAG (neodymium-doped yttrium aluminum garnet) laser therapy.\(^\text{11}\) Response rates (ie, 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%-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.\(^\text{12}\) 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=0.002\ [\text{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.\(^\text{13}\) 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.

**EARLY-STAGE LUNG CANCER**

**Clinical Context and Test Purpose**
The purpose of PDT in patients who have early-stage lung cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with early-stage lung cancer?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients with early-stage NSCLC who are not candidates for surgery or 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.

**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.

**Timing**
Tumor response can be assessed within weeks to months. Assessment of response rates, recurrence, and disease-free survival requires longer follow-up.

**Setting**
PDT is administered in a tertiary care setting.

**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. Evidence on PDT for early lung cancer consists of case series.
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Case Series
The prescribing information for porfimer sodium (Photofrin) has described 3 case series of 62 patients with microinvasive lung cancer.\(^5\) 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; and 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.\(^14\) 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. PDT for Treatment of Early-Stage NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results (95% CI)</th>
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| FDA (Photofrin prescribing information) (2011)\(^5\) | Microinvasive, inoperable endobronchial tumors | 62 | • CR at 3 mo: 50%  
| | | | • Median survival: 2.9 y (2.1 to 5.7)  |
| Endo et al (2009)\(^15\) | Centrally located early lung cancer; longitudinal tumor length ≤10 mm | 48 | • 5-y survival: 81%  
| | | | • CR=94%  |
| Moghissi et al (2007)\(^16\) | Early central lung cancer, ineligible for surgery | 21 | • CR=100%  |
| Corti et al (2007)\(^17\) | Early inoperable or recurrent NSCLC | 40 | • CR=72%  
| | | | • PR=20%  
| | | | • NR=6%  
| | | | • Median survival: 91 mo  |
| Furukawa et al (2005)\(^18\) | Early-stage, central-type lung cancers | 93 | Lesion <1 cm:  
| | | | • CR=93%  
| | | | • 5-y survival: 58%  
| | | | Lesion ≥1 cm:  
| | | | • CR=58%  
| | | | • 5-y survival: 59%  |
| Kato et al (1996)\(^14\) | Early-stage, central-type lung cancers | 95 | CR=83%  |


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.\(^19\) 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, 24-116 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 HGD

Clinical Context and Test Purpose
The purpose of PDT in patients 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 question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with Barrett esophagus with HGD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients with Barrett esophagus with HGD.

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 for Barrett esophagus with HGD: radiofrequency ablation, surveillance, esophagectomy, and cryotherapy.

Outcomes
The general outcomes of interest are symptom relief, response rate, and progression of cancer.

Timing
Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival requires longer follow-up.

Setting
PDT is administered in a tertiary care setting.

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).³ 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. 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. 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 be confirmed by an expert gastrointestinal pathologist. Patients randomized to the treatment group received up to 3 courses of PDT separated by 90 days. The primary efficacy end point was the 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). 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<0.001) 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=0.027), with a significantly longer time to progression with PDT. Serious complications were reported by 12% of PDT patients vs 1% 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-mediated PDT for the treatment of 64 patients with Barrett esophagus with HGD. (Note: Oral ALA does not have FDA approval as a photosensitizing agent for PDT.) Patients were recruited from a single university hospital in England. At 1 year, 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 (p=0.62). 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, one in the 5-ALA group and two in the porfimer group. Overall cancer incidence was 12% and 17% in the 5-ALA and porfimer groups, respectively (p=0.240). Strictures (26% vs 7%) and photosensitivity (43% vs 6%) were more common with porfimer. Pleural effusions (7% vs 18%) and transaminitis (0% vs 47%) were more common with 5-ALA.
Observational Studies
Prasad et al (2007) conducted a retrospective chart review of patients who received PDT (n=129) or surgery (n=70) for HGD in Barrett esophagus. Overall mortality rates were 9% and 8.5% in the PDT and surgery groups, respectively, over a median follow-up of 59 months for the PDT group and 61 months for the surgery group.

Section Summary: Barrett Esophagus With HGD
One RCT comparing PDT plus a proton pump inhibitor with a proton pump inhibitor alone demonstrated that a higher response rate and a lower risk of progression to cancer persisted during the 5-year follow-up for PDT; however, long-term follow-up is only available for a small number of patients. In addition, PDT patients had significantly more complications, including a high rate of strictures. Observational comparative data have suggested similar mortality outcomes for PDT and esophagectomy over 5 years.

CHOLANGIOCARCINOMA

Clinical Context and Test Purpose
The purpose of PDT in patients who have cholangiocarcinoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with cholangiocarcinoma?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with unresectable cholangiocarcinoma.

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 overall survival.

Timing
Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival requires longer follow-up. Note that long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting.

Setting
PDT is administered in a tertiary care setting.

Systematic Reviews
Several systematic reviews (NIHR [2010], Gao et al [2010], Tomizawa and Tian [2012], Lu et al [2015]) have evaluated the use of PDT as an adjunct to stenting for the treatment of
cholangiocarcinoma. The reviews identified 2 RCTs and several nonrandomized trials. The 2 RCTs were
considered good-to-moderate quality although the sample sizes were small (N=32, N=39). The
nonrandomized studies were considered low-to-moderate quality. Porfimer sodium (Photofrin) was the
photosensitizing agent used in all but two of the included studies. The most commonly reported adverse
events were cholangitis (28%), phototoxicity (10%), and biloma (2%). One review conducted a meta-
analysis (Lu et al [2015]) that showed patients receiving PDT plus stenting experienced significantly
longer OS (hazard ratio, 0.49; 95% CI, 0.33 to 0.73; p<0.01) than patients receiving stenting only. The 2
RCTs are discussed below.

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. Median survival of the 20
patients in the PDT group was 493 days compared with 98 days in the 19 patients who underwent
stenting alone. The trial was terminated prematurely due to these favorable results.

Zoepf et al (2005) randomized 32 patients with cholangiocarcinoma to stenting with and without PDT.
Median survival was 21 months for the PDT group compared with 7 months in the control group.

Hauge et al (2016) reported on results of a phase 2 safety and feasibility RCT for combination
chemotherapy plus stenting with and without temoporfin (Foscan) PDT in the treatment of biliary tract
cancer. Eligible patients had unresectable or recurrent/metastatic biliary tract cancer, no previous
chemotherapy or radiotherapy for the current cancer, and no other cancers in the previous 5 years.
Twenty patients were enrolled; 17 had hilar cholangiocarcinoma. In the PDT group, 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 EORTC
QLQ-C30 symptom score (range, 0-100) was 33 vs 24 for the fatigue domain, 14 vs 19 for the nausea and
vomiting domain, and 14 vs 10 for the pain domain for PDT vs no PDT, respectively. Precision estimates
were not given. Median progression-free survival was 139 days (range, 26-600 days) with PDT vs 96 days
(range, 56-422 days) without PDT. Median OS was 238 days (range, 178-1060) in the PDT group and 336
days (range, 110-690 days) in the no-PDT group.

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

Kahaleh et al (2008) retrospectively evaluated 19 patients treated with endoscopic retrograde
cholangiopancreatography (ERCP) with PDT and stents, and 29 patients treated with ERCP and stents
alone at a U.S. center. All patients had unresectable cholangiocarcinoma; most had Bismuth type III
and IV lesions (involvement of left and/or right secondary hepatic ducts). Some patients in each group
received chemoradiotherapy. Mortality rates at 3, 6, and 12 months were 0%, 16%, and 56%,
respectively, in the PDT plus stent group, and 28%, 52%, and 82%, respectively, in the stent-alone group.
Differences were statistically significant at 3 and 6 months. The authors noted that “it remains to be
proved whether this effect is attributable to PDT or the number of ERCP sessions, and a randomized
multicenter study is required to confirm these data.”
In a comparative review with concurrent controls, Witzigmann et al (2006) analyzed records of 184 patients treated over a 10-year period in Germany for hilar cholangiocarcinoma. Sixty patients underwent resection (8 after neoadjuvant PDT), 68 had PDT plus stenting, and 56 had stenting alone. Median survival was 12 months in the PDT plus stenting group vs 6.4 months in the stent-alone group (p<0.01). Patients who received PDT plus stenting had lower serum bilirubin levels (p<0.05) and higher Karnofsky Performance Status scores (p<0.01).

Several case series have reported positive quality of life outcomes with PDT. In 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. On the negative side, he noted that PDT is not available at all centers and requires expertise in both endoscopy and PDT; laser fibers available in the United States are suboptimal for ERCP use—because of their stiffness, treatment is limited to the main hepatic ducts; the procedure is time-consuming; and posttreatment photosensitivity lasts for 4 to 6 weeks, potentially limiting quality of life. In favor of PDT, the procedure is reasonably well-tolerated, seems to be effective, can be repeated without a ceiling dosage effect, and is the only treatment to date for which data suggest improved survival over plastic stent placement alone for advanced cholangiocarcinoma. Baron 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: Cholangiocarcinoma
Several observational studies and 2 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 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 Test Purpose
The purpose of PDT in patients who have other malignancies such as gynecologic cancers, bladder cancer, head and neck cancers, brain cancer, soft tissue sarcoma, and mesothelioma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PDT improve the net health outcomes in patients with malignancies such as gynecologic cancers, bladder cancer, head and neck cancers, brain cancer, soft tissue sarcoma, and mesothelioma?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients with gynecologic cancers, bladder cancer, head and neck cancers, brain cancer, soft tissue sarcoma, 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 following therapies are currently being used to make decisions about other malignancies: response rate, recurrence rate, and survival.

**Timing**
Symptom relief and tumor response can be assessed within weeks to months. Recurrence and survival requires longer follow-up.

**Setting**
PDT is administered in a tertiary care setting.

**Gynecologic Malignancies**
Godoy et al (2013) reported on a retrospective cohort of women with recurrent gynecologic malignancies treated at a single U.S. center; 32 patients with recurrent gynecologic malignancies (9 cervical, 6 vulvar, 6 vaginal, 5 ovarian, 5 endometrial, 1 recurrent Paget disease of the anal canal) were treated with porfimer-mediated PDT.\(^{37}\) Five (24%) of 21 patients who had vaginal, cervical, or anal recurrences achieved complete response (defined as a lack of detectable lesions within the area of treatment). Median time to response was 28 months. Some patients received more than 1 treatment. Patients with vaginal and cervical recurrences also had moderate-to-severe burning sensation, with maximum treatment for 3 weeks.

**Endometrial Cancer**
In a retrospective Korean cohort study, Choi et al (2013) investigated the use of PDT as a fertility-sparing treatment for patients with early-stage (confined to the endometrium) endometrial cancer.\(^{38}\) Sixteen patients were treated with PDT for grade 1 or 2 disease (mean age, 31 years; range, 24-35 years). The photosensitizing agent was Photogem (non-FDA-approved) administered intravenously. Mean follow-up from diagnosis was 78 months (range, 8-140 months). After initial PDT, 12 (75%) of 16 patients showed complete response (defined as complete disappearance of adenocarcinoma or hyperplasia on follow-up dilation and curettage), and 4 patients were nonresponders. Four (33%) of the 12 initial responders experienced recurrence 6 months after complete response; 2 responded after additional PDT treatments. One of 4 initial nonresponders achieved complete response after a second PDT treatment. Seven patients attempted to become pregnant, all initial responders. Four (57%) patients had 7 pregnancies, four with artificial reproductive technology and three by natural means, resulting in 6 live births. All were by cesarean delivery. No evidence of endometrial cancer recurrence or hyperplasia was found before or after childbirth. In a similar study, Choi et al (2014) retrospectively reviewed 21 patients, ages 45 years 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.\(^{39}\) This treatment was considered a fertility-preserving alternative to vaginal radical trachelectomy (excision of the uterine cervix). 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, five 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 papilloma virus (HPV) infection. 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, 2.5; 95% CI, 1.2 to 5.1) and HPV infection (odds ratio, 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 placebo.

Tao et al (2014) in China published a systematic review of PDT for CIN. Literature was searched through March 2012, and 14 studies, mostly cohort studies and case series, were included (total N=472 patients). Criteria for PDT efficacy varied across studies, but most (10/14) required biopsy. Overall, 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. 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 the patient response at 3 months, defined by regression of CIN and clearance of oncogenic HPV. After blinded central pathology review, 79% of randomized patients were confirmed as having CIN grade 1 or 2 and were included in efficacy analyses. Of these patients, 49% with CIN grade 1 and 83% with CIN grade 2 had oncogenic HPV infection. Statistically significant differences in complete response at 3 months compared with placebo were observed only for patients with CIN grade 2 who received 5% HAL (18 [95%] of 19 patients vs 12 [57%] of 21 patients; p=0.009). All responders in both groups, maintained response 6 months after last treatment. Five (2%) of 262 randomized women became pregnant within 3 months of last treatment, and all delivered healthy full-term infants. Interpretation of these results was limited by the lack of randomization among patients included in efficacy analyses and lack of statistical correction for multiple testing.

Case Series
In a study included in the Tao systematic review, Istomin et al (2010) reported on 112 patients with morphologically proven CIN grades 2 and 3 with at least 1 year of follow-up after treatment with Photolon (a non-FDA-approved photosensitizing agent) PDT. Complete regression of neoplastic lesions was seen in 104 (93%) treated women. Of 88 patients infected with highly oncogenic strains of HPV, 47 (53%) had complete eradication of HPV infection 3 months after treatment. Fifteen women became pregnant after treatment and recovery; live births occurred in 8 cases, six by vaginal and two by cesarean delivery.

Subsequent to the literature search of the Tao review, Soergel et al (2012) reported on 72 patients with histologically confirmed CIN grade 1, 2, or 3 who were treated with PDT at a single center in Germany. Patients were randomized to 1 of 6 treatment groups defined by varying dosages of the photosensitizing agent, HAL or methylaminolevulinate (neither FDA-approved for systemic use). The primary end point was complete response at 6 months, defined as normal histology and cytology. Women treated with...
HAL 40 mM applied twice in 3 hours (vs 12 hours) followed by a light dose of 50 to 100 J/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.\(^{45}\) At baseline, 95% of patients were symptomatic; at 52 weeks, 65% of patients were asymptomatic.

**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.\(^{46}\) 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).\(^{47}\) 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.\(^{48}\) Twenty-six studies (total N=988 patients; range, 2-147 patients) of several different photosensitizers were included (ALA, meta-tetrahydroxyphenylchlorin [Foscan], hematoporphyrin derivatives, Photofrin, Photosan, and chlorin e6). 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.\(^{49}\) 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 (total N=276 patients) evaluating PDT for treatment of head and neck cancer.\(^3\) 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.\(^{50}\) Of 5 studies included, one was a series of 135 patients, which reported 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.\(^{51}\) 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, \(p=0.75\)), 5-year local recurrence-free survival (67% vs 74%; \(p=0.13\)), or OS (83% vs 75%; \(p=0.17\)).

**Noncomparative Studies**

Ahn et al (2016) reported on outcomes of a phase 1 study of PDT with ALA for premalignant and early-stage head and neck tumors.\(^{52}\) 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.\(^{53}\) Of 115 patients in this case series who had recurrent or primary carcinoma in situ, T1N0 and T2N0, the 5-year cure rate was 100%; at mean follow-up of 91 months, 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 three months of PDT, had conventional neck dissection, and were disease-free for at least five years. In 48 patients treated for superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity, there were 5 recurrences, all salvaged with repeat PDT or surgical resection. The 3-year cure rate was 100% (mean follow-up, 56 months).

Several small (sample size range, 7-30 patients), uncontrolled studies have been reported on PDT for laryngeal, oral, and nasopharyngeal cancers.\(^{54-55}\) Different outcomes were reported across studies. Of the studies reporting response rates, complete response was observed in 67% to 100% of patients treated with PDT. Two studies collected data on OS. One of them reported a 4-year OS rate of 67%\(^{57}\) and the other reported a 5-year OS rate of 36%.\(^{56}\)

**Brain Cancer**

The NIHR systematic review (2010) identified 2 trials using PDT to treat brain cancer.\(^3\) 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 ALA-PDT to treat patients with glioblastoma multiforme. Patients receiving the resection plus PDT experienced significantly longer survival (52.8 weeks vs 24.2 weeks) and significantly longer time to recurrence (8.6 months 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).\(^{60}\) 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). Of the patients with lung cancer metastases, one died of an unrelated cause, and six were free of brain disease until death. Two of the remaining patients (one with metastatic bowel cancer, one with unknown primary) died of local brain recurrence.

**Soft Tissue Sarcoma**

In a retrospective, single-center study from Japan, Matsubara et al (2013) examined PDT in high-grade soft tissue sarcoma. Acridine orange (a non-FDA-approved fluorescent dye) was used as the photosensitizer in 51 PDT-treated patients. Compared with 119 patients who underwent conventional wide-margin resection for limb salvage surgery, there was no statistical difference in 10-year OS (p=0.75) or 10-year local recurrence (p=0.36).

**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. 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. 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. Median follow-up was 5.3 years, with 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 interpretation of the results.

**Other Applications**

PDT has been used for the treatment of pancreatic cancer, obstructive jaundice due to hepatocellular carcinoma, and oral premalignant lesions. There is little evidence of PDT’s efficacy for these indications.

**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 rate 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 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 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 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 soft tissue sarcoma 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 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.

SUMMARY OF EVIDENCE

For individuals who have obstructing esophageal cancer who receive PDT as palliation, the evidence includes systematic reviews, RCTs, and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. A meta-analysis comparing PDT with Nd:YAG laser suggested that improvements in dysphagia are similar, although estimates are imprecise. Compared with the Nd:YAG laser, PDT is associated with a lower risk of perforation and a higher risk of adverse reactions to the light (eg, photosensitivity). PDT plus argon plasma coagulation appears to prolong the time to recurrence of dysphagia as opposed to argon plasma coagulation alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have obstructing endobronchial lesions who receive PDT as palliation, the evidence includes RCTs and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Evidence from RCTs comparing PDT with Nd:YAG laser has generally supported reductions in symptoms using PDT similar to those using a laser. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy who receive PDT, the evidence includes uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. There are few patients with early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy. While several treatment methods (eg, laser, electrocautery, cryotherapy, brachytherapy) are available for this population, studies comparing the treatment methods are not available. Case series of PDT include between 21 and 95 patients and have reported complete response rates ranging from 72% to 100%. Given the small size of this potential population and the ineligibility for standard surgical treatment or radiotherapy, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have Barrett esophagus with high-grade dysplasia who receive PDT, the evidence includes an RCT and observational studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The RCT compared PDT plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression with cancer persisting during 5 years of follow-up for
patients in the PDT group. The results of the RCT also revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Observational comparative data have suggested similar mortality outcomes for PDT and esophagectomy over 5 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable cholangiocarcinoma who receive PDT plus stenting as palliation, the evidence includes systematic reviews, RCTs, and observational studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Two small RCTs and several observational studies have found that PDT plus stenting is associated with the 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 overall survival, with similar adverse event rates. Case series have suggested an improvement in quality of life with PDT. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small size of this potential population, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other malignancies (eg, gynecologic, bladder, head and neck, brain, soft tissue) who receive PDT, the evidence includes controlled observational studies and uncontrolled single-arm studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The published literature on PDT for these malignancies is generally comprised of small case series without comparator groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**American College of Chest Physicians**
The American College of Chest Physicians (2013) updated its evidence-based guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways. 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 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 recommended PDT as an option for treatment of confirmed high-grade dysplasia (HGD) with Barrett esophagus.
American College of Gastroenterology
The 2015 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 HGD.\(^7\) 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.”

National Comprehensive Cancer Network

**Esophageal Cancer and Barrett Esophagus**
National Comprehensive Cancer Network (NCCN) guidelines (v.2.2018) 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.\(^7\) 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**
NCCN guidelines on hepatobiliary cancers (v.1.2018) 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)\(^2\) and Zoepf et al (2005)\(^2\)].”\(^7\)

**Non-Small-Cell Lung Cancer**
NCCN guidelines (v.4.2018) 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 endobronchial obstruction or severe hemoptysis.\(^1\)

National Institute for Health and Care Excellence
The 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,\(^7\) treatment of localized inoperable endobronchial cancer,\(^7\) and treatment of advanced bronchial carcinoma\(^7\) 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,\(^7\) early-stage esophageal cancer,\(^7\) and bile duct cancer.\(^7\)
- 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.\(^8\) 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.\(^8\)
Society of Thoracic Surgeons
The Society of Thoracic Surgeons published practice guidelines (2009) on the management of Barrett esophagus with HGD. The guidelines stated 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.

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 unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT01755013</td>
<td>Open-label Observational Study of Plastic Cylindrical Fiber Optic Diffuser (Pioneer Optics) in Photodynamic Therapy for the Management of Cholangiocarcinoma</td>
<td>55</td>
<td>Mar 2018 (ongoing)</td>
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<tr>
<td>NCT02153229</td>
<td>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</td>
<td>102</td>
<td>May 2018 (ongoing)</td>
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<tr>
<td>NCT02628665</td>
<td>Two-Arm Phase III Trial Comparing Different Time of Endoscopic Photodynamic Therapy on Esophageal and/or Gastric Cardiac Cancer</td>
<td>40</td>
<td>Dec 2019</td>
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<tr>
<td>NCT03090412</td>
<td>A Randomized Multicenter Phase II Study Using (2-1[Heyloxyethyl]-2-Devinylypyropheophorbide-a) (HPPH) With PDT Versus Standard of Care Surgery for Patients With T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity</td>
<td>114</td>
<td>Nov 2021</td>
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<tr>
<td><strong>Unpublished</strong></td>
<td></td>
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<td></td>
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<tr>
<td>NCT00587600</td>
<td>Biomarkers in Phototherapy of Barrett's Esophagus</td>
<td>208</td>
<td>Sep 2017</td>
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</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td>96570</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>96571</td>
<td>As above; each additional 15 minutes</td>
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<tr>
<td>HCPCS</td>
<td>J9600</td>
<td>Porfimer sodium, 75 mg</td>
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</table>

_original Policy Date:_ December 1995
MP 8.01.06
Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

ICD-10-CM | C15.3-C15.9 | Malignant neoplasm of esophagus code range
          | C16.0        | Malignant neoplasm of cardia (includes cardio-esophageal junction)
          | C22.1        | Intrahepatic bile duct carcinoma (includes cholangiocarcinoma)
          | C34.00-C34.92| Malignant neoplasm of bronchus and lung code range
          | C78.7        | Secondary malignant neoplasm of liver and intrahepatic bile duct
          | D01.5        | Carcinoma in situ of liver, gallbladder and bile ducts;
          | C78.00-C78.02| Secondary malignant neoplasm of lung code range
          | C78.80-C78.89| Secondary malignant neoplasm of other and unspecified digestive organs code range
          | D00.1        | Carcinoma in situ of esophagus
          | D02.20-D02.22| Carcinoma in situ of bronchus and lung code range
          | K22.711      | Barrett's esophagus with high grade dysplasia

ICD-10-PCS | ICD-10-PCS codes are only used for inpatient services. There are no ICD 10 PSC codes for this procedure

Type of Service | Therapy
Place of Service | Inpatient/Outpatient

POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>03/13/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through February 15, 2014; references 16, 28-29, 33-41, 47-48, 53-57, and 59 added; references 3 and 62-72 updated. No change to policy statements.</td>
</tr>
<tr>
<td>03/12/15</td>
<td>Replace policy</td>
<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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<tr>
<td>02/24/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review; no change to policy.</td>
</tr>
<tr>
<td>08/30/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to policy as noted; effective 11/15/2017. Policy updated with literature review through June 2, 2017; references 2, 15-18, 28, 31, 49, 53, and 73 added; multiple guidelines updated. Policy statements changed to include treatment for unresectable cholangiocarcinoma as medically necessary.</td>
</tr>
<tr>
<td>07/25/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through May 7, 2018; references 40 and 65 added. Policy statements unchanged.</td>
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