Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 10/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Photodynamic Therapy for Subfoveal Choroidal Neovascularization, Dermatologic Applications of Photodynamic Therapy and Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus are addressed separately in medical policies 00097, 00098 and 00261, respectively.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider one or more courses of photodynamic therapy (PDT) for oncologic applications to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for photodynamic therapy (PDT) for oncologic applications will be considered when any of the following criteria are met:

- Palliative treatment of obstructing esophageal cancer; or
- Palliative treatment of obstructing endobronchial lesions; or
- Treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy; or
- Treatment of high-grade dysplasia in Barrett's esophagus; or
- Palliative treatment of unresectable cholangiocarcinoma when used with stenting

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of photodynamic therapy (PDT) for oncologic applications when patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers other oncologic applications of photodynamic therapy (PDT) including, but not limited to, other malignancies and Barrett's esophagus without associated high-grade dysplasia to be **investigational.***

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Background/Overview

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. For patients with early-stage disease, surgery is the standard treatment. For inoperable early non-small-cell lung cancer, treatment guidelines from the National Comprehensive Cancer Network recommend stereotactic ablative radiotherapy. The guidelines reference a 2009 phase 2 multicenter noncomparative trial of stereotactic body radiotherapy assessing 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's Esophagus

The esophagus is normally lined by squamous epithelium. Barrett's esophagus is a condition in which the normal squamous epithelium is replaced by specialized columnar-type epithelium known as intestinal metaplasia, in response to irritation and injury caused by gastroesophageal reflux disease (GERD). Barrett's esophagus occurs in the distal esophagus, may be of any length, focal or circumferential, and can be visualized on endoscopy with a different color than the background squamous mucosa. Confirmation of Barrett's esophagus requires biopsy of the columnar epithelium and microscopic identification of intestinal metaplasia.

Intestinal metaplasia is a precursor to esophageal adenocarcinoma, and patients with Barrett's esophagus are at a 40-fold increased risk for developing this disease compared to the general population. Esophageal adenocarcinoma is thought to result from a stepwise accumulation of genetic abnormalities in the specialized epithelium, which results in the phenotypic expression of histologic features of low-grade dysplasia to high-grade dysplasia (HGD) to carcinoma. Most patients with nondysplastic Barrett esophagus do not progress beyond nondysplasia; the estimated rate of progression is 0.9% per patient per year. In comparison, the rate of progression from low-grade dysplasia to either HGD or esophageal adenocarcinoma ranges from 0.5% to 13.4% per patient per year. Once HGD is present, the risk of

developing adenocarcinoma is 2% to 10% per patient per year; approximately 40% of patients with HGD on biopsy are found to have associated carcinoma in the resection specimen.

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 prognosis is generally poor due to 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.

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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The indications of the U.S. FDA label for porfimer sodium as of June 2011 are as follows:
Esophageal cancer

- Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy

Endobronchial cancer

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

High-grade dysplasia in Barrett's esophagus

- Treatment of HGD in Barrett's esophagus patients who do not undergo esophagectomy

As of June 2018, oral 5-ALA has not received FDA approval as a photosensitizing agent for PDT. Topical 5-aminolevulinic acid, used for the treatment of actinic keratoses, is addressed separately.

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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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 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. 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. 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 [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. 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.

Case Series
The prescribing information for porfimer sodium (Photofrin) has described 3 case series of 62 patients with microinvasive lung cancer. 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. 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

Study	Population	N	Results (95% CI)
FDA (Photofrin prescribing information) (2011)	Microinvasive, inoperable endobronchial tumors	62	• CR at 3 mo: 50% • Median survival: 2.9 y (2.1 to 5.7)
Endo et al (2009)	Centrally located early lung cancer; longitudinal tumor length ≤10 mm	48	• 5-y survival: 81% • CR=94%
Moghissi et al (2007)	Early central lung cancer, ineligible for surgery	21	• CR=100%
Corti et al (2007)	Early inoperable or recurrent NSCLC	40	• CR=72% • PR=20%

Study	Population	N	Results (95% CI)
			• NR=6% • Median survival: 91 mo
Furukawa et al (2005)	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)	Early-stage, central-type lung cancers	95	CR=83%

CI: confidence interval; CR: complete response; 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. 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 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). 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. 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. 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. 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. 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.[43] 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. 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. 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). 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. 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. 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. 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. 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. 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 PTD with ALA for premalignant and early-stage head and neck tumors. 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. 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. 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%.

Brain Cancer

The NIHR systematic review (2010) identified 2 trials using PDT to treat brain cancer. 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). 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.[65] 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.[69] 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 along 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus", 8.01.06, 7:2018.
2. Fayter D, Corbett M, Heirs M et al. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess 2010; 14(37):1-288.
3. Spechler SJ, Sharma P, Souza RF et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology 2011; 140(3):1084-91.
4. Pinnacle Biologics. Photofrin® (porfimer sodium injection) prescribing information, June 2011. Available online at: http://www.pinnaclebiologics.com/our-products/photofrinreg-prescribing-information. Last accessed February, 2014.
5. Li LB, Xie JM, Zhang XN et al. Retrospective study of photodynamic therapy vs photodynamic therapy combined with chemotherapy and chemotherapy alone on advanced esophageal cancer. Photodiagnosis and photodynamic therapy 2010; 7(3):139-43.
6. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2014;10:CD005048.
7. McCann P, Stafinski T, Wong C et al. The safety and effectiveness of endoscopic and non-endoscopic approaches to the management of early esophageal cancer: a systematic review. Cancer treatment reviews 2011; 37(1):11-62.
8. Rupinski M, Zagorowicz E, Regula J et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). The American journal of gastroenterology 2011; 106(9):1612-20.
9. Diaz-Jimenez JP, Martinez-Ballarin JE, Llunell A et al. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 1999; 14(4):800-5.
10. Moghissi K, Dixon K, Stringer M et al. The place of bronchoscopic photodynamic therapy in advanced unresectable lung cancer: experience of 100 cases. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 1999; 15(1):1-6.
11. Akopov A, Rusanov A, Gerasin A, et al. Preoperative endobronchial photodynamic therapy improves resectability in initially irresectable (inoperable) locally advanced non-small cell lung cancer. Photodiagnosis Photodyn Ther. Sep 2014; 11 (3):259-264. PMID 24704942
12. Kato H, Okunaka T, Shimatani H. Photodynamic therapy for early stage bronchogenic carcinoma. Journal of clinical laser medicine & surgery 1996; 14(5):235-8.
13. Cortese DA, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung. Mayo Clinic proceedings. Mayo Clinic 1997; 72(7):595-602.
14. Konda VJ, Waxman I. Endotherapy for Barrett's esophagus. The American journal of gastroenterology 2012; 107(6):827-33.
15. Overholt BF, Wang KK, Burdick JS et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointestinal endoscopy 2007; 66(3):460-8.
16. Badreddine RJ, Prasad GA, Wang KK et al. Prevalence and predictors of recurrent neoplasia after ablation of Barrett's esophagus. Gastrointestinal endoscopy 2010; 71(4):697-703.
17. Pech O, Behrens A, May A et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008; 57(9):1200-6.
18. Prasad GA, Wang KK, Buttar NS et al. Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. Gastroenterology 2007; 132(4):1226-33.
19. Dunn JM, Mackenzie GD, Banks MR et al. A randomised controlled trial of ALA vs. Photofrin photodynamic therapy for high-grade dysplasia arising in Barrett's oesophagus. Lasers Med Sci 2013; 28(3):707-15.
20. Tomizawa Y, Tian J. Photodynamic therapy for unresectable cholangiocarcinoma. Dig Dis Sci 2012; 57(2):274-83.
21. Shim CS, Cheon YK, Cha SW et al. Prospective study of the effectiveness of percutaneous transhepatic photodynamic therapy for advanced bile duct cancer and the role of intraductal ultrasonography in response assessment. Endoscopy 2005; 37(5):425-33.
22. Harewood GC, Baron TH, Rumalla A et al. Pilot study to assess patient outcomes following endoscopic application of photodynamic therapy for advanced cholangiocarcinoma. Journal of gastroenterology and hepatology 2005; 20(3):415-20.
23. Berr F. Photodynamic therapy for cholangiocarcinoma. Seminars in liver disease 2004; 24(2):177-87.

24. Ortner ME, Caca K, Berr F et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology 2003; 125(5):1355-63.
25. Zoepf T, Jakobs R, Arnold JC et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. The American journal of gastroenterology 2005; 100(11):2426-30.
26. Pereira SP, Aithal GP, Ragunath K et al. Safety and long term efficacy of porfimer sodium photodynamic therapy in locally advanced biliary tract carcinoma. Photodiagnosis and photodynamic therapy 2012; 9(4):287-92.
27. Gao F, Bai Y, Ma SR et al. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. Journal of hepato-biliary-pancreatic sciences 2010; 17(2):125-31.
28. Kahaleh M, Mishra R, Shami VM et al. Unresectable cholangiocarcinoma: comparison of survival in biliary stenting alone versus stenting with photodynamic therapy. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 2008; 6(3):290-7.
29. Witzigmann H, Berr F, Ringel U et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. Ann Surg 2006; 244(2):230-9.
30. Baron TH. Photodynamic therapy: standard of care for palliation of cholangiocarcinoma? Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2008; 6(3):266-7.
31. Godoy H, Vaddadi P, Cooper M et al. Photodynamic therapy effectively palliates gynecologic malignancies. European journal of gynaecological oncology 2013; 34(4):300-2.
32. Choi MC, Jung SG, Park H et al. Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long-term follow-up study. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 2013; 23(4):698-704.
33. Choi MC, Jung SG, Park H, et al. Fertility preservation by photodynamic therapy combined with conization in young patients with early stage cervical cancer: a pilot study. Photodiagnosis Photodyn Ther. Sep 2014; 11(3):420-425. PMID 24927981
34. Tao XH, Guan Y, Shao D, et al. Efficacy and safety of photodynamic therapy for cervical intraepithelial neoplasia: a systemic review. Photodiagnosis Photodyn Ther. Jun 2014; 11 (2):104-112. PMID 24631593
35. Hillemanns P, Petry KU, Soergel P, et al. Efficacy and safety of hexaminolevulinate photodynamic therapy in patients with low-grade cervical intraepithelial neoplasia. Lasers Surg Med. Aug 2014;46(6):456-461. PMID 24799181
36. Soergel P, Dahl GF, Onsrud M et al. Photodynamic therapy of cervical intraepithelial neoplasia 1-3 and human papilloma virus (HMV) infection with methylaminolevulinate and hexaminolevulinate--a double-blind, dose-finding study. Lasers Surg Med 2012; 44(6):468-74.
37. Istomin YP, Lapzevich TP, Chalau VN et al. Photodynamic therapy of cervical intraepithelial neoplasia grades II and III with Photolon. Photodiagnosis and photodynamic therapy 2010; 7(3):144-51.
38. Winters U, Daayana S, Lear JT et al. Clinical and immunologic results of a phase II trial of sequential imiquimod and photodynamic therapy for vulval intraepithelial neoplasia. Clinical cancer research : an official journal of the American Association for Cancer Research 2008; 14(16):5292-9.
39. Bader MJ, Stepp H, Beyer W et al. Photodynamic therapy of bladder cancer - a phase I study using hexaminolevulinate (HAL). Urologic oncology 2013; 31(7):1178-83.
40. Lee JY, Diaz RR, Cho KS et al. Efficacy and safety of photodynamic therapy for recurrent, high grade nonmuscle invasive bladder cancer refractory or intolerant to bacille Calmette-Guerin immunotherapy. The Journal of urology 2013; 190(4):1192-9.
41. de Visscher SA, Dijkstra PU, Tan IB et al. mTHPC mediated photodynamic therapy (PDT) of squamous cell carcinoma in the head and neck: a systematic review. Oral Oncol 2013; 49(3):192-210.
42. Silbergleit AK, Somers ML, Schweitzer VG et al. Vocal fold vibration after photofrin-mediated photodynamic therapy for treatment of early-stage laryngeal malignancies. Journal of voice: official journal of the Voice Foundation 2013; 27(6):762-4.
43. Wildeman MA, Fles R, Herdini C et al. Primary treatment results of Nasopharyngeal Carcinoma (NPC) in Yogyakarta, Indonesia. PloS One 2013; 8(5):e63706.
44. Stoker SD, van Diessen JN, de Boer JP et al. Current treatment options for local residual nasopharyngeal carcinoma. Current treatment options in oncology 2013; 14(4):475-91.
45. Durbec M, Cosmidis A, Fuchsmann C et al. Efficacy and safety of photodynamic therapy with temoporfin in curative treatment of recurrent carcinoma of the oral cavity and oropharynx. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2013; 270(4):1433-9.

46. Rigual NR, Shafirstein G, Frustino J et al. Adjuvant intraoperative photodynamic therapy in head and neck cancer. JAMA otolaryngology-- head & neck surgery 2013; 139(7):706-11.
47. Rigual NR, Thankappan K, Cooper M et al. Photodynamic therapy for head and neck dysplasia and cancer. Archives of otolaryngology--head & neck surgery 2009; 135(8):784-8.
48. Schweitzer VG, Somers ML. PHOTOFRIN-mediated photodynamic therapy for treatment of early stage (Tis-T2N0M0) SqCCa of oral cavity and oropharynx. Lasers Surg Med 2010; 42(1):1-8.
49. Biel MA. Photodynamic therapy treatment of early oral and laryngeal cancers. Photochemistry and photobiology 2007; 83(5):1063-8.
50. Karakullukcu B, Stoker SD, Wildeman AP et al. A matched cohort comparison of mTHPC-mediated photodynamic therapy and trans-oral surgery of early stage oral cavity squamous cell cancer. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2013; 270(3):1093-7.
51. Wildeman MA, Nyst HJ, Karakullukcu B et al. Photodynamic therapy in the therapy for recurrent/persistent nasopharyngeal cancer. Head & neck oncology 2009; 1:40.
52. Matzi V, Maier A, Woltsche M et al. Polyhematoporphyrin-mediated photodynamic therapy and decortication in palliation of malignant pleural mesothelioma: a clinical pilot study. Interactive cardiovascular and thoracic surgery 2004; 3(1):52-6.
53. Lindenmann J, Matzi V, Neuboeck N et al. Multimodal therapy of malignant pleural mesothelioma: is the replacement of radical surgery imminent? Interactive cardiovascular and thoracic surgery 2013; 16(3):237-43.
54. Muragaki Y, Akimoto J, Maruyama T et al. Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors. Journal of neurosurgery 2013; 119(4):845-52.
55. Aziz F, Telara S, Moseley H et al. Photodynamic therapy adjuvant to surgery in metastatic carcinoma in brain. Photodiagnosis and photodynamic therapy 2009; 6(3-4):227-30.
56. Eljamel S. Photodynamic applications in brain tumors: a comprehensive review of the literature. Photodiagnosis and photodynamic therapy 2010; 7(2):76-85.
57. Nomura T, Mimata H. Focal therapy in the management of prostate cancer: an emerging approach for localized prostate cancer. Adv Urol 2012; 2012:391437.
58. Wolff JM, Mason M. Drivers for change in the management of prostate cancer - guidelines and new treatment techniques. BJU Int 2012; 109 Suppl 6:33-41.
59. Barret E, Ahallal Y, Sanchez-Salas R et al. Morbidity of focal therapy in the treatment of localized prostate cancer. European urology 2013; 63(4):618-22.
60. Eymerit-Morin C, Zidane M, Lebdai S et al. Histopathology of prostate tissue after vascular-targeted photodynamic therapy for localized prostate cancer. Virchows Archiv : an international journal of pathology 2013; 463(4):547-52.
61. Azzouzi AR, Barret E, Moore CM et al. TOOKAD((R)) Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer. BJU Int 2013; 112(6):766-74.
62. Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clinical oncology (Royal College of Radiologists (Great Britain)) 2013; 25(8):461-73.
63. Matsubara T, Kusuzaki K, Matsumine A et al. Can a less radical surgery using photodynamic therapy with acridine orange be equal to a wide-margin resection? Clinical orthopaedics and related research 2013; 471(3):792-802.
64. Pereira S. Photodynamic therapy for pancreatic and biliary tract cancer: the United Kingdom experience. J Natl Compr Canc Netw. Oct 1 2012;10 Suppl 2:S48-51. PMID 23055216
65. Huggett MT, Jermyn M, Gillams A, et al. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. Br J Cancer. Apr 2 2014;110 (7):1698-1704. PMID 2456946
66. Bahng S, Yoo BC, Paik SW et al. Photodynamic therapy for bile duct invasion of hepatocellular carcinoma. Photochemical & photobiological sciences: Official journal of the European Photochemistry Association and the European Society for Photobiology 2013; 12(3):439-45.
67. FV MCD, Al-Kheraif AA, Qadri T, et al. Efficacy of photodynamic therapy in the management of oral premalignant lesions. A systematic review. Photodiagnosis Photodyn Ther. Oct 11 2014. PMID 25315968
68. Wisnivesky JP, Yung RC, Mathur PN, et al. Diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. May 2013;143 (5 Suppl):e263S-277S. PMID 23649442.

69. Babjuk M, Böhle A, Burger M et al. European Association of Urology. Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS). Uroweb 2014. http://www.uroweb.org/guidelines/online-guidelines/. Accessed February 16, 2015.
70. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Esophageal and esophagogastric junction cancer (V.1.2015). http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed January 20, 2015.
71. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Hepatobiliary cancers (V.2.2015). http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed February 12, 2015.
72. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Non-small cell lung cancer (V.4.2015). http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed February 12, 2015.
73. National Institute for Health and Clinical Excellence. IPG206 Palliative photodynamic therapy for advanced oesophageal cancer-guidance. 2007; http://www.nice.org.uk/nicemedia/pdf/IPG206guidance.pdf. Accessed January 20, 2015.
74. National Institute for Health and Clinical Excellence. IPG137 Photodynamic therapy for localized inoperable endobronchial cancer-guidance. 2005; http://www.nice.org.uk/guidance/ipg137. Accessed January 20, 2015.
75. National Institute for Health and Clinical Excellence. IPG87 Photodynamic therapy for advanced bronchial carcinoma-guidance. 2004; http://guidance.nice.org.uk/IPG87/Guidance/pdf/English. Accessed January 20, 2015.
76. National Institute for Health and Clinical Excellence. IPG259 Interstitial photodynamic therapy for malignant parotid tumours-guidance. 2008; http://www.nice.org.uk/nicemedia/pdf/IPG259Guidance.pdf. Accessed January 20, 2015.
77. National Institute for Health and Clinical Excellence. IPG200 Early-stage Oesophageal cancer-guidance. 2006; http://www.nice.org.uk/nicemedia/pdf/IPG200guidance.pdf. Accessed January 20, 2015.
78. National Institute for Health and Clinical Excellence. IPG134 Bile duct cancer-guidance. 2005; http://www.nice.org.uk/guidance/IPG134/Guidance/pdf. Accessed January 20, 2015.
79. National Institute for Health and Clinical Excellence. IPG350 Photodynamic therapy for Barrett's oesophagus-guidance. 2010; http://www.nice.org.uk/guidance/ipg350. Accessed February 12, 2015.
80. National Institute for Health and Clinical Excellence. IPG290 Photodynamic therapy for brain tumours-guidance. 2009; http://www.nice.org.uk/nicemedia/pdf/IPG290Guidance.pdf. Accessed January 20, 2015.
81. Fernando HC, Murthy SC, Hofstetter W, et al. The Society of Thoracic Surgeons practice guideline series: guidelines for the management of Barrett's esophagus with high-grade dysplasia. Ann Thorac Surg. Jun 2009;87(6):1993-2002. PMID 19463651
82. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. Jul 10 2009;27(20):3290-3296. PMID 19414667
83. Furukawa K, Kato H, Konaka C, et al. Locally recurrent central-type early stage lung cancer < 1.0 cm in diameter after complete remission by photodynamic therapy. Chest. Nov 2005;128(5):3269-3275. PMID 16306036
84. Corti L, Toniolo L, Boso C, et al. Long-term survival of patients treated with photodynamic therapy for carcinoma in situ and early non-small-cell lung carcinoma. Lasers Surg Med. Jun 2007;39(5):394-402. PMID 17565719
85. Moghissi K, Dixon K, Thorpe JA, et al. Photodynamic therapy (PDT) in early central lung cancer: a treatment option for patients ineligible for surgical resection. Thorax. May 2007;62(5):391-395. PMID 17090572
86. Endo C, Miyamoto A, Sakurada A, et al. Results of long-term follow-up of photodynamic therapy for roentgenographically occult bronchogenic squamous cell carcinoma. Chest. Aug 2009;136(2):369-375. PMID 19318660
87. Lu Y, Liu L, Wu JC, et al. Efficacy and safety of photodynamic therapy for unresectable cholangiocarcinoma: A meta-analysis. Clin Res Hepatol Gastroenterol. Dec 2015;39(6):718-724. PMID 26070572
88. Hauge T, Hauge PW, Warloe T, et al. Randomised controlled trial of temoporfin photodynamic therapy plus chemotherapy in nonresectable biliary carcinoma--PCS Nordic study. Photodiagnosis Photodyn Ther. Mar 2016;13:330-333. PMID 26415549
89. Gondivkar SM, Gadbail AR, Choudhary MG, et al. Photodynamic treatment outcomes of potentially-malignant lesions and malignancies of the head and neck region: A systematic review. J Investig Clin Dent. May 08 2017. PMID 28480637
90. Ahn PH, Quon H, O'Malley BW, et al. Toxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumors. Oral Oncol. Apr 2016;55:37-42. PMID 26865261
91. Babjuk M, Compérat E, Gontero P, et al. Non-muscle-invasive Bladder Cancer (European Association of Urology). 2017; http://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/. Accessed August 9, 2017.
92. Zhang W, Zhang A, Sun W, et al. Efficacy and safety of photodynamic therapy for cervical intraepithelial neoplasia and human papilloma virus infection: A systematic review and meta-analysis of randomized clinical trials. *Medicine (Baltimore).* May 2018;97(21):e10864. PMID 29794788

93. Friedberg JS, Simone CB, 2nd, Culligan MJ, et al. Extended pleurectomy-decortication-based treatment for advanced stage epithelial mesothelioma yielding a median survival of nearly three years. *Ann Thorac Surg.* Mar 2017;103(3):912-919. PMID 27825687

Policy History

Original Effective Date: 03/18/2009
Current Effective Date: 10/17/2018

03/04/2009	Medical Director review
03/18/2009	Medical Policy Committee approval. New policy.
03/05/2010	Medical Policy Committee approval
03/19/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated rationale and references.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage.
10/01/2016	Coding update
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Policy statements changed to include treatment for unresectable cholangiocarcinoma as eligible for coverage.
01/01/2018	Coding update
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 10/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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

Code Type	Code
CPT	31641, 43229, 96570, 96571
HCPCS	J9600 Code added eff 1/1/2018: J7345
ICD-10 Diagnosis	C15.3-C15.9, C22.1, C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92, C49.A0-C49.A2, C78.00-C78.02, C78.7-C78.89, D00.1-D00.2, D02.20-D02.22

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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