Protocol

Oncologic Applications of Photodynamic Therapy, Including Barrett Esophagus

(80106)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 05/19
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Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With obstructing esophageal cancer	Interventions of interest are: • Photodynamic therapy as palliation	Comparators of interest are: • Stenting • Laser therapy • Argon plasma coagulation	Relevant outcomes include: • Change in disease status • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With obstructing endobronchial lesions	Interventions of interest are: • Photodynamic therapy as palliation	Comparators of interest are: • Laser therapy • Brachytherapy • External-beam radiotherapy • Resection	Relevant outcomes include: • Change in disease status • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With early-stage non-small-cell lung cancer who are not candidates for surgery or	Interventions of interest are: • Photodynamic therapy	Comparators of interest are: • Radiofrequency ablation • Cryotherapy • Brachytherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Treatment-related morbidity
Individuals: • With Barrett esophagus with high-grade dysplasia	Interventions of interest are: • Photodynamic therapy	Comparators of interest are: • Radiofrequency ablation • Surveillance • Esophagectomy • Cryotherapy	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Treatment-related morbidity
Individuals: • With unresectable cholangiocarcinoma	Interventions of interest are: • Photodynamic therapy plus stenting as palliation	Comparators of interest are: • Stenting alone	Relevant outcomes include: • Change in disease status • Symptoms • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With other malignancies	Interventions of interest are: • Photodynamic therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Treatment-related morbidity

DESCRIPTION

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

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. PDT is associated with a lower risk of perforation compared with Nd:YAG laser treatment; however, PDT runs a higher risk that a patient might react adversely to the light (e.g., 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 cancer 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 improvements in symptoms with PDT similar to those with laser. The evidence is sufficient to deter-mine 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; additionally, several treatment methods are available for this population. Studies comparing these 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 to cancer persisting during five years of follow-up for PDT. The results of the RCT revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Observational comparative data suggested similar mortality outcomes for PDT and esophagectomy over five 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 greater elimination of bile duct stenosis and improved survival benefit than 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 rates of adverse events. 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 (e.g., 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 small case series without comparator groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

BACKGROUND

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.

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. There are several nonsurgical approaches to provide palliation of dysphagia including PDT.

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. 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.[1] 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 three-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 (e.g., 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 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.[3] 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.[4] 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.[3]

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

PHOTODYNAMIC THERAPY

Several photosensitizing agents have been used in PDT: porfimer sodium (Photofrin), administered intravenously 48 hours before light exposure, and 5-aminolevulinic acid (5-ALA), administered orally four to six hours before the procedure. 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, Bannockburn, IL), as approved by the U.S. Food and Drug Administration (FDA) 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.

High-Grade Dysplasia in Barrett Esophagus

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

As of June 2017, oral 5-ALA has not received FDA approval as a photosensitizing agent for PDT. Topical 5-ALA, used for treatment of actinic keratoses, is addressed separately (see the Dermatologic Applications of Photodynamic Therapy Protocol).

This protocol 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.

RELATED PROTOCOLS

Dermatologic Applications of Photodynamic Therapy

Endoscopic Radiofrequency Ablation or Cryoablation for Barrett Esophagus

Photodynamic Therapy for Choroidal Neovascularization

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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