Photodynamic Therapy for Patients with Advanced Non–Small-Cell Carcinoma of the Lung

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Abstract

Patients with advanced non–small-cell lung carcinoma (NSCLC) have poor prognoses and experience negative sequelae of disease. Patients often suffer from dyspnea and/or hemoptysis, with overall pulmonary compromise. Patients with advanced, inoperable disease have limited options for treatment. This study summarizes our early experience and findings using photodynamic therapy (PDT) as an effective modality in the palliation of hemoptysis, dyspnea, and physical airway obstruction in cases of inoperable lung cancer. A retrospective review was conducted for the first 10 patients diagnosed with stage III/IV obstructive NSCLC who underwent PDT at our institution. Endobronchial lesions were identified by bronchoscopy. Treatments were initiated 48 hours after intravenous injection of 2 mg/kg of the photosensitizing agent porfimer sodium (Photofrin, QLT PhotoTherapeutics, Vancouver, BC). The porfimer sodium was then activated by illumination with a 630 nm wavelength light using a Coherent argon ion laser through a flexible bronchoscope. Repeated bronchoscopies were performed 1-3 days following initial PDT for evaluation and airway debridement. In 8 cases, a second treatment of PDT was administered within 72 hours of the first injection. One patient received a third treatment several months later. Three patients also received endobronchial stents after PDT. Overall, all 10 patients responded to PDT. Physical airway obstruction was reduced in all patients, with a noted improvement in bronchoscopic luminal diameter. Acute hemoptysis resolved in all 7 symptomatic patients. Median survival was 5.5 months post-PDT, while median survival postdiagnosis was 10.5 months. Three patients are alive at the time of this review at 5-21 months following therapy. Patients with unresectable late-stage NSCLC have few options for treatment. Our early experience with PDT indicates effective relief of hemoptysis, dyspnea, and airway obstruction and improves their quality of life.

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Introduction

Lung cancer is the leading cause of cancer death in the United States.[1] Recent studies show that as many as 76% of newly diagnosed non–small-cell lung cancer (NSCLC) cases are classified as stage III/IV.[2] Consequently, most patients have a poor chance of receiving curative treatment, so therapy is aimed at palliation.

Patients often present with significant symptoms of disease at the time of diagnosis. Patients with end-stage disease may present with sequelae of airway obstruction such as dyspnea, exercise intolerance, recurrent pneumonias, and hemoptysis.[3-5] Frequently, they present in some distress and can rapidly progress to respiratory failure. Such patients require invasive supportive care and palliative intervention.

Regardless of presentation or condition, stage III/IV lung cancer patients face significant morbidity, reduction in quality of life, and certain mortality.[6,7] Physicians and patients are left with few options for definitive treatment and/or palliation. Chemotherapy, radiation, and neodymium:yttrium-aluminum-garnet (Nd-YAG) laser treatment are all available for tumor containment, debulking, and slowing of disease progression.[8-11] Surgical excision has not been proven to significantly extend survival for such patients.[12,13]

Photodynamic therapy (PDT), though an old concept, has gained recent focus and approval for use in the treatment of early-stage unresectable endobronchial lung cancer and pallia-

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Table 1 Patient Characteristics

Patient	Age (Years)/Sex	Type	Location of Lesion
1	48/ Male	Stage IIIB adenocarcinoma	RMS bronchus
2	76/Male	Stage IV adenocarcinoma	Trachea, LMS and LLL bronchi
3	76/Male	Stage IIIB adenocarcinoma	RLL and RML bronchi
4	62/Female	Stage IV adenocarcinoma	RMS, RUL, and RML bronchi
5	64/Female	Stage IV squamous cell carcinoma	LMS and LLL bronchi
6	74/Female	Stage IIIB adenocarcinoma	LLL bronchus
7	63/Male	Stage IV adenoid cystic carcinoma	Trachea
8	65/Male	Stage IIIB squamous cell carcinoma	Bronchus intermedius, RMS bronchus
9	65/Male	Stage IV adenocarcinoma	Trachea
10	75/Male	Stage IV adenocarcinoma	Bronchus intermedius

Abbreviations: LLL = left lower lobe; LMS = left main stem; RLL = right lower lobe; RML = right middle lobe; RMS = right main stem; RUL = right upper lobe

tion of advanced obstructing masses.[14-18] PDT involves the use of a highly photosensitive porfimer sodium substance (Photofrin™, QLT PhotoTherapeutics, Vancouver, BC) that is systemically given to the patient and is selectively taken up by tumor beds.[19] Laser irradiation induces selective tumor cell death by processes not entirely understood.

The purpose of this study is to summarize our early experience with PDT in the palliation of symptoms in patients with terminal lung cancer and obstructing endobronchial lesions.

Methods

PDT was initiated at The University of California, Irvine, Medical Center. This retrospective study summarizes our experience with the first 10 patients from August 1998 through December 2000. The procedures were performed in cooperation between the cardiothoracic surgery, pulmonary medicine, and anesthesiology services.

Ten patients with a mean age of 67 years (48-76 years) underwent PDT for 1 or more treatment cycles. Patients were identified for treatment based upon staging and symptoms. All patients were stage III/IV and nonoperable (Table 1). Two of the patients had tracheal lesions that were treated. All patients were inpatients with significant preprocedure (periprocedure) disease morbidity and had significant symptoms/sequelae of disease.

Anesthesia

The laser irradiation portion of PDT was performed in a specialized bronchoscopy suite. Full consent was obtained and care was taken in accordance with hospital policy. Patients were premedicated with midazolam. American Society of Anesthesiologists standard monitors (5-lead EKG, noninvasive blood pressure cuff, and pulse oximeter) were placed. A peripheral intravenous line and in some cases a radial arterial line were placed. Anesthetic induction was carried out using propofol, and patients were intubated with an endotracheal tube (n = 10). During laser maneuvers, jet ventilation was carried out through closed-circuit standard ventilators (n = 4) or open-ended endotracheal tubes using 100% oxygen (n = 6). Anesthesia was maintained using propofol, muscle relaxant, and/or fentanyl. During bronchoscopy, when closed-circuit ventilation was permitted, additional anesthesia was administered using inhaled anesthetics. End tidal carbon dioxide measurements, pulse oximetry, and arterial blood gas sampling assured that patients maintained proper oxygenation and ventilation during the procedure.

Laser Irradiation

Patients selected for PDT received porfimer sodium (2.0 mg/kg) intravenously approximately 48 hours prior to laser treatment. Patients were secluded from light for 6 weeks after porfimer sodium administration due to skin hyperphotosensitivity.

After the induction of general endotracheal anesthesia, patients were placed in the supine position. All patients underwent an initial flexible bronchoscopic examination through the endotracheal tube. After localization of the bronchial lesion, the laser tip was positioned by bronchoscopic visualization with fluoroscopic confirmation (Figures 1 and 2). The 2 patients who had tracheal lesions received laser dosing through the clear wall of the endotracheal tube itself.

The 630-nm wavelength laser irradiation was generated by a Coherent Lambda Plus PD L1 argon ion laser (Santa Clara, CA). A 1.0-cm and/or 2.5-cm diffusing quartz tip fiber was used on the bronchoscope to direct and deliver an average of 200 J/cm light per treatment session, depending on the length of the endobronchial tumor (Figure 2).

Patients received follow-up flexible bronchoscopy for debridement and evaluation of treatment. Eight of the 10 patients received follow-up PDT within 72 hours of the original porfimer sodium injection.

Results

The mean time from diagnosis of lung cancer to treatment

with PDT was 135 days. The 2 patients with the greatest time period between diagnosis and PDT (515 days and 325 days) initially received radiation and chemotherapy. The mean survival for our patient group was 10.5 months postdiagnosis and 5.5 months post-PDT. Three patients are alive at the time of this study, living 21 months, 14 months, and 5 months post-PDT.

Technical Synopsis

PDT was performed successfully on 10 patients via flexible fiberoptic bronchoscopy. Most lesions were centrally located in primary conducting airways; thus, advancement and positioning of the diffusing fiber was not difficult. No peripheral or occult lesions were treated in this group of patients. Nine of 10 patients received 2 treatments with the same porfimer sodium injection, with a similar and significant response at both sessions. No significant, acute complications were encountered directly during flexible bronchoscopy or laser irradiation.

In addition to PDT, endobronchial stents were used on 3 patients. One patient, who remains alive, received an endobronchial stent 10 months after PDT. The other 2 patients received stents within 3 months of PDT.

Response to Therapy

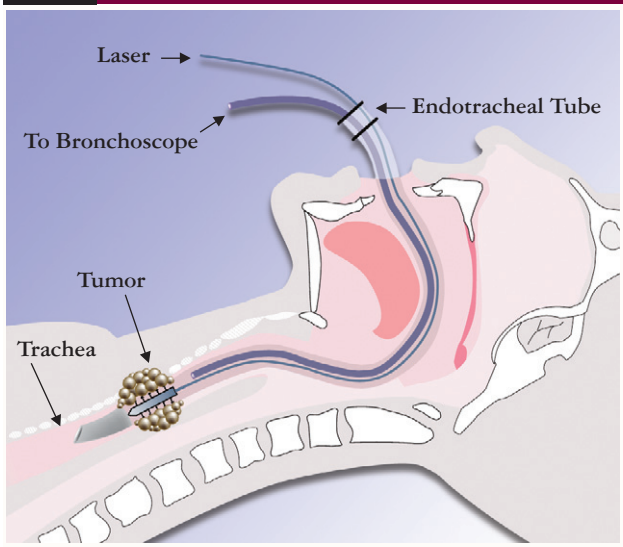
Generally, all obstructing endobronchial tumor types responded to PDT by gross examination and by subjective response through patient symptoms (Table 2). Physical airway obstruction was reduced in all patients, with a noted improvement in bronchoscopic luminal diameter. Subjective symptoms of obstruction (dyspnea) were improved in 9 of 10 patients who were awake. Acute hemoptysis resolved in all 7 symptomatic patients, and in cases where nonoccult hemoptysis could be visualized with the bronchoscope, complete hemostasis was appreciated by the end of laser irradiation.

Two patients were treated for midtracheal lesions. Both had 90% obstructing tumor masses with significant symptomatology. After securing the patient airway by advancing a smaller endotracheal tube through and beyond the lesion, laser irradiation was successfully delivered through the clear wall. Both patients experienced a reduction in tumor to less than 50% obstruction. One patient was extubated in less than 24 hours and was discharged 3 days after PDT. This patient later went on to undergo resection of his tumor and tracheal reconstruction and is alive at the time of this study. The other patient had similar results with very significant reduction in tumor size; however, he expired from an existing, invasive fungal infection (disseminated aspergillosis) several days after PDT. *Aspergillus* was identified in the necrotic tracheal tumor at postmortem examination.

Postprocedural Care and Complications

All patients undergoing PDT experienced similar reactions to treatment. All developed significant tissue swelling and inflammation in the areas irradiated by laser. Subsequently, tumor beds became necrotic and sloughed thereafter. Patients were kept intubated for airway protection and to allow for follow-up debridement bronchoscopy. Each patient underwent an average of 2 debridement bronchoscopies after PDT. One patient had significant continuous sloughing of tumor that required numerous ICU bedside serial bronchoscopies and aggressive pulmonary toilet for approximately 24 hours post-PDT.

Figure 1 Diagramatic Illustration of Endotracheal PDT Administration



Patients who were intubated electively at the time of the procedure remained intubated an average of 2 days (range, < 12 hours-4 days) post-PDT (Table 3). Four patients were intubated prior to therapy secondary to respiratory failure. Comorbid diagnoses were related to their obstructing lesions (ie, postobstructive pneumonia, hypercapnia, hypoxia). These 4 patients remained intubated an average of 16 days (range, 3-30 days) post-PDT.

Discussion

Photodynamic therapy is a readily available treatment modality at the University Medical Center. Three pulmonologists and 2 thoracic surgeons are trained and work collaboratively in the

Figure 2 Negative/Inverted Image Showing PDT Administration Through Endotracheal Tube

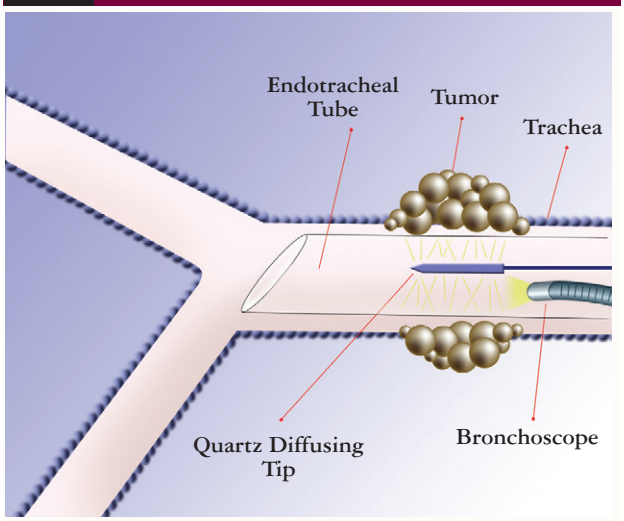


Table 2 Response to PDT

Patient	Indication	Post-PDT Early Response	Recurrence
1	Obstruction, hemoptysis, dyspnea	Decreased: hemoptysis, obstruction, dyspnea	Hemoptysis, dyspnea - 4 months
2	Obstruction, hemoptysis, dyspnea	No hemoptysis; Decreased: obstruction, dyspnea	Dyspnea - 0.5 months
3	Obstruction, hemoptysis	No hemoptysis; Decreased: obstruction, dyspnea	Dyspnea - 2 months
4	Obstruction, dyspnea	Decreased: obstruction	None
5	Obstruction, dyspnea	Decreased: obstruction, dyspnea; 2nd - decreased: obstruction	Obstruction, dyspnea - 3 months
6	Obstruction, dyspnea	Decreased: obstruction, hemoptysis, dyspnea	Hemoptysis - 6 months Dyspnea - 12 months
7	Obstruction, dyspnea	Decreased: obstruction, hemoptysis, dyspnea	Hemoptysis - 3 months
8	Obstruction, hemoptysis, dyspnea	Decreased: obstruction, hemoptysis, dyspnea	Obstruction, dyspnea - 6 months
9	Obstruction, hemoptysis, dyspnea	Decreased: obstruction, hemoptysis	None
10	Obstruction, hemoptysis, dyspnea	Decreased: obstruction, hemoptysis, dyspnea	Hemoptysis, dyspnea - 3.5 months

Abbreviation: PDT = photodynamic therapy

diagnosis and treatment of lung cancer patients who may benefit from this procedure. A special endoscopy suite is reserved and equipped to perform PDT, and an ICU is equipped with flexible bronchoscopy and supportive staff experienced in dealing with patients after this treatment.

After performing PDT on the first 10 patients, we realized that PDT was technically simple to administer in centrally located lesions. Every patient responded with varying resolution of symptoms and improvement of respiratory function. All patients received more than 1 treatment with no periprocedural complications.

PDT induced a remarkable airway inflammatory response in all 10 patients. Airways became locally edematous, and malignant tissues sloughed. Most of these patients required close monitoring, aggressive pulmonary toilet, and easy mobilization for follow-up bronchoscopy for debridement. Failure to eradicate all tumor tissue in the affected airways made necessary the need for subsequent stent placement. Furthermore, some patients required prolonged intubation and respiratory support until sequelae resolved. However, cooperation among the team members allowed prudent management of hospital resources while providing aggressive palliative care to these terminal patients.

All of the patients presented with clinically significant symptoms related to late-stage lung cancer. Palliation was necessary and was our goal for the use of PDT. In most of these patients, PDT relieved the clinical symptoms that initially prompted hospitalization. However, the use of PDT in this small group

Table 3 Morbidity/Mortality of Advanced Lung Cancer Patients Following PDT

Patient	Time Intubated Post-PDT	Survival after Diagnosis	Survival Post-PDT
1	10 days	4 months	4.1 months - deceased
2	4 days	4 months	0.5 months - deceased
3	3 days	5 months	2 months - deceased
4	21 days	18 months	0.75 months - deceased
5	**1st:** 2 days; **2nd:** 10 days	13 months	2.75 months - deceased
6	2 days	26 months+	21 months - alive at study
7	< 12 hours	5 months+	5 months - alive at study
8	1 day	10 months+	14 months - alive at study
9	3 days	3 months	0.25 months - deceased
10	30 days	8 months	5 months - deceased

Abbreviation: PDT = photodynamic therapy

showed no significant change in an expected survival for stage III/IV lung cancer. Of the 4 acutely ill patients who were treated with PDT, 2 became ventilator independent and were discharged from the hospital.

In addition, major tracheal lesions were successfully treated by laser irradiation through the endotracheal tube. We demonstrated that tracheal lesions were treatable by maneuvering an endotracheal tube through the lesion and positioning the laser diffuser inside the endotracheal tube for optimal dosing. The endotracheal tube also assured a patent airway during the period after therapy. Of the 2 patients treated via this technique, 1 is still alive and has undergone subsequent resection of his tumor.

Our early experience suggests that PDT is a low-risk, readily available procedure for selected nonresectable stage III/IV NSCLC patients. Successful reduction of airway obstruction, with resultant resolution of hemoptysis and dyspnea, ultimately improves quality of life for terminally ill lung cancer patients.

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