Photodynamic Therapy in Lung Cancer

By David Ost, MD [3]

Photodynamic therapy (PDT) involves the use of photosensitizing agents that are selectively retained within tumor cells. The agents remain inactive until exposed to light of the proper wavelength. When activated by light, these

Introduction

Photodynamic therapy (PDT) involves the use of photosensitizing agents for the treatment of malignant disease. These photosensitizing agents are infused intravenously and are selectively retained within tumor cells. When exposed to light of the proper wavelength, the photosensitizing agent is activated. This leads to the formation of toxic oxygen radicals, which result in cell death.

Until recently, PDT for lung cancer had primarily been a research tool. Several institutions worked with PDT in the 1980s, but its use in the United States remained limited to the research setting. Photodynamic therapy using the first FDA-approved photosensitizing agent, porfimer sodium (Photofrin), is now available to US clinicians.

Photodynamic therapy has the potential to complement and improve the approach to a variety of clinical problems. Potential applications include carcinoma in situ, early-stage lung cancer in nonsurgical candidates, advanced lung cancer, and tumors metastatic to the lung. To properly assess the role of PDT in these settings requires careful analysis of the mechanism of action and technique of PDT, a review of clinical studies using PDT, and an exploration of how PDT may be integrated into a multimodality approach.

Mechanism of Action

The concept of photochemical sensitization and subsequent cell death is not a new one. Light was used for healing by the ancient Greeks, and by 1900 photochemical reactions were used to kill paramecia.

Photodynamic therapy was initially used to treat skin cancers in the early 1900s, leading to a variety of chemicals being developed to promote photochemical cytotoxicity.[1] Among the agents used, hematoporphyrin subsequently demonstrated the ability to be selectively concentrated or preferentially retained within malignant cells.[2,3] Hematoporphyrin derivatives were later shown, first by Lipson et al and then by Gregorie et al, to be retained in a large percentage of squamous cell carcinomas and adenocarcinomas.[4-8] This led to the development of newer hematoporphyrin derivatives with experimental applications, including breast cancer and bladder cancer, and the use of PDT in an even wider spectrum of malignancies.[9-13]

These pioneering studies highlighted the importance of several factors related to the mechanism of PDT: membrane injury, delivery of oxygen, the role of the immune and vascular systems, the importance of the photosensitizer, and light dosimetry. Each of these factors is critical to the mechanism of action of PDT and has potential clinical implications.

Membrane Injury

The basic mechanism of the cellular cytotoxicity of PDT seems to be membrane damage. The plasma and mitochondrial membranes, in particular, are targets of PDT because of the water-lipid partition coefficient of the photosensitizing agents.[14-19] Porphyrin uptake studies demonstrate initial binding of the photosensitizing agent with the plasma membrane, with subsequent extension to the internal cellular membranes.[20] Damage occurs after light activation and is visible immediately. Initially, the damage is characterized by the formation of multiple areas of membrane injury, or blebs. These progress to form larger balloon-like areas.[16,21] Cellular division and normal functions cease; this is followed by cell lysis.

Concurrent with damage to the plasma membrane is injury to other internal cellular membranes, including the mitochondrial membrane, nuclear membrane, Golgi apparatus, and endoplasmic
With mitochondrial injury comes inhibition of oxidative phosphorylation and generation of adenosine triphosphate (ATP), followed by a decrease in cellular ATP.[22,23] Using phosphate-31 spectroscopy to assess metabolic response to PDT, it can be shown that the fall in ATP is dramatic, becoming virtually undetectable 2 to 4 hours after treatment.[24,25] Although PDT results in nuclear membrane injury and DNA strand breaks, it does not appear that DNA injury plays an important role in cell death. Importantly, PDT has not been shown to be mutagenic in vitro.[16,19,26]

**Delivery of Oxygen**

In vitro, when oxygen is not present or is present in a concentration of less than 2%, cells become resistant to PDT.[27,28] The cytotoxicity of PDT is free radical-mediated via a type II photooxidation reaction.[16,19] In type II reactions, light energy excites and activates the photosensitizer, energy transfer occurs from the sensitizer in its excited state to molecular oxygen, and singlet oxygen species are generated.[29] The resulting free radical generation leads to the membrane injury described above.

The importance of free radical-mediated injury is underscored by the observation that scavengers of singlet oxygen, such as 1,3-diphenylisobenzofuran, reduce PDT-mediated cytotoxicity.[30] Low oxygen concentrations have also been shown to lead to decreased sensitivity to PDT in vitro, and tissue hypoxia models in animals support this observation. Other investigators have suggested that local tumor hypoxia may account for some cases of nonresponsiveness to PDT.

Thus, all of the membrane injury described above is predicated on the availability of an adequate concentration of oxygen to generate free radicals.

**Role of the Immune and Vascular Systems**

Part of the in vivo tumor destruction results from the effect of PDT on the vasculature. The neovasculature of tumors may be a target for PDT since these venous-derived vessels may not have sufficient strength to remain patent in the face of high extravascular pressures. Decreased flow occurs, leading to arteriolar and venular stasis, arteriolar vasoconstriction, thrombosis of venules, and increasing interstitial edema.[31,32] In addition, other investigators have hypothesized and demonstrated varying degrees of increased coagulation in the vascular bed associated with PDT. Studies with nuclear magnetic resonance imaging using in situ fluorine have shown that damage to the tumor vasculature occurs prior to actual tumor necrosis.[33] Ben-Hur and Orenstein demonstrated increased coagulation associated with injury to the endothelium from PDT, with resultant red blood cell agglutination and thrombus formation.[34]

Associated with this complex picture of free radical injury, vascular injury, and coagulation is a concurrent immune response, characterized by platelet and neutrophil activation.[16,35] This immune activation results in the release of vasoactive compounds, including arachidonic acid derivatives, such as prosta-glandins E\textsubscript{2} and I\textsubscript{2} and thromboxane. The potential contribution of these mediators to cell death and tumor injury has been demonstrated by the observation that cyclooxygenase inhibitors reduce the effect of PDT on arterioles.[36]

Thus, in addition to oxygen-mediated free radical membrane injury and ATP depletion, both direct vascular damage and immune-mediated injury may contribute to cell death from PDT.

**Photosensitizers**

A wide variety of photosensitizing agents have been studied and developed, including the chlorins, phthalocyanines, tetraphenylporphine sulfate, porphines, rhodamine-123, and porphyrin-based agents. The clinically significant aspects of photosensitizers include their relative concentration in tumors, their yield of singlet oxygen, the amount of tissue penetration allowed, and their photostability/lability.

The only photosensitizing agent that has been approved by the FDA—porfimer sodium (Photofrin)—belongs to the porphyrin-based family of agents. Consequently, this discussion will focus on porfimer sodium, although many of the comments apply to other agents currently under investigation.

Selective retention or uptake of the photosensitizer by tumors allows for a relatively high tumor-tissue concentration ratio. Most sensitzers have a concentration ratio ranging from 2:1 to 5:1. The selective tumor retention associated with the porphyrin-based agents was initially reported by Figge in 1948.[2] Lipson and colleagues subsequently demonstrated that derivatives of hematoporphyrin were associated with an even higher tumor-tissue concentration ratio.[4-8] This tumor-tissue ratio is highest at 24 to 48 hours after intravenous injection. However, Lipson and colleagues also demonstrated that fluorescence could be detected within 3 hours of intravenous injection. This has clinical importance in terms of how photoactive agents are
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used. When employed for lung cancer treatment (ie, PDT), the time interval between injection and light application is typically 48 to 72 hours. When used in investigational studies for tumor detection and localization, the 3-hour time interval is more useful.

The mechanism of selective retention and uptake of the porphyrins is based on studies using murine models, which demonstrated that these photosensitizers are accumulated and retained by endocytosis via the vascular endothelium.[16,35,37] This is due, in part, to the lipophilic nature of the compounds, previously described in relation to their propensity to bind to cell membranes based on their partition coefficient.

The distribution pattern of porphyrins after intravenous infusion mirrors that of low-density lipoprotein receptors in the various organs, with the greatest amount found in the liver, followed, in descending order, by the adrenal glands, urinary bladder, pancreas, kidney, spleen, stomach, bone, lung, heart, muscle, and brain.[38] The serum half-life of photosensitizing agents in humans is 20 to 30 hours, but these compounds may persist in the skin at low levels of 2% to 5% for up to 4 to 6 weeks.[39]

The exact mechanism of selective retention of photosensitizing agents remains an area of investigation. Possible theories include: increased tumor uptake of low-density lipoprotein-associated sensitizers; increased uptake by tumors due to their lower pH, and the associated increase in water solubility of the sensitizer at low pH; poor lymphatic drainage of tumors; tumor angiogenesis factors: and changes within the stromal cells of tumors that increase uptake.[16,35]

As described above, the cytotoxicity of PDT is mediated via a complex set of interactions, including photooxidative reactions. The photosensitizer must be able to absorb photons of appropriate wavelengths so as to become a triplet species. The light-excited triplet state of the sensitizer transfers its energy to endogenous state triplet oxygen to produce an excited state of molecular oxygen, singlet oxygen. This is the type II photooxidation reaction described above. Importantly, singlet oxygen can be generated with quantum energies as low as 0.98 MeV, corresponding to a wavelength of 1,220 nm. However, most available sensitizers work efficiently only at wavelengths up to 850 nm, with a quantum yield of 0.2 to 0.6 MeV.[40]

The differences in quantum yield appear to be related, or at least affected by, the location of the sensitizer in the cells. In addition, for any given quantum yield, lipophilic sensitizers, such as porfimer sodium, seem to be more efficient than hydrophilic sensitizers at similar quantum yields. Thus, while these considerations may seem esoteric, they have direct clinical impact in terms of efficacy.

Furthermore, the quantum energy used relates to the important clinical issue of tissue penetration. The wavelength, as determined by the quantum energy used, directly affects the maximum absorbance capacity and depth of tissue penetration of the photosensitizing agent. With respect to the porphyrin family of photosensitizers, the absorption spectra demonstrate a peak at 405 nm. Use of this peak allows for fluorescence of tumors to be used as a tumor marker. However, for treatment (PDT), this wavelength of light is suboptimal, since it is nearly completely absorbed within 1 mm of the surface. Thus, a wavelength of 630 nm is used for PDT. This allows for penetration to a depth of approximately 5 mm.

Obviously, the development of future photosensitizers will be greatly affected by consideration of the quantum energies used, their absorption spectra, and the resultant clinical consequences, in terms of depth of penetration.

Finally, all photosensitizers can be destroyed by light, which may have an impact on cytotoxicity. When exposed to light, a sensitizer may generate enough energy to destroy tumor tissue but be destroyed and lose its cytotoxic potential within normal cells, a process described as photobleaching. This effect is an important consideration, since it allows minimal damage to adjacent normal tissue while selectively destroying tumor cells.

Light Dosimetry

The efficacy of PDT depends on accurate delivery of light to the area to be treated. It is useful to think of PDT in terms of three components: (1) the photosensitizer’s characteristics and concentration at the tumor site (described above), (2) the rate of energy delivery (power), and (3) the total energy delivered.

With respect to the delivery of light, any source of light with the appropriate characteristics could be used. In practice, laser light is typically used because it offers the advantage of a uniform spectrum and coherence. For lung cancer, the argon dye pump or excimer laser is often used, although, in theory, any laser with the proper wavelength and power could be employed. Important in vivo considerations include the effect of dose rate delivery and total energy delivery.
Although in vitro evidence has suggested that a high dose rate (power) is associated with improved cytotoxicity, in vivo data have demonstrated that lower dose rates may be more effective.[41,42] In a study involving the treatment of human mesothelioma allografts in nude mice, decreasing the light intensity from 200 to 50 mW/cm² actually improved response. The investigators hypothesized that a reduction in the fluence rate or fractionation may paradoxically enhance the effect of treatment because of an increase in singlet oxygen in regions of poor capillary flow. Regardless of whether this is the only mechanism involved, what is clearly important is the empiric observation that light dosimetry has a clinical impact on response and side effects. Thus, controlled, reproducible light dosimetry and the technology used to deliver it are important considerations for PDT.

Method

The method of PDT is a result of its mechanisms of action and other factors, as described above. Based on the mechanism of action, one can anticipate that PDT will require at least two distinct steps: delivery of the photosensitizer and subsequent activation with laser light. In lung cancer, this is usually followed by a third step consisting of bronchoscopic removal of necrotic debris.

Infusion of the Photosensitizer

Infusion of the photosensitizer is accomplished through a simple peripheral intravenous infusion of porfimer sodium at a dose of 2 mg/kg. After the infusion, the patient becomes photosensitive and remains so for 1 month. Therefore, careful instruction must be given prior to therapy regarding appropriate avoidance of direct sunlight. Indoor light poses no problem. Typically, a handbook containing written instructions is distributed to patients prior to the infusion, along with concurrent verbal instructions.

Light Activation of the Photosensitizer

For porfimer sodium, the wavelength of light used for activation is 630 nm. This is accomplished with an appropriate laser system delivered via a bronchoscope. The laser fibers can be tailored to fit the clinical situation, with cleaved probes for forward light projection, bulbous tips for isotropic spherical distribution, or cylindrical coatings for light perpendicular to the axis of the fiber. The fiber can be inserted into endobronchial tumors directly (interstitial delivery) or placed alongside the tumor. Based on clinical experience and limited published clinical studies, we prefer to use cylindrical light-diffusing fibers when working within the bronchi. The reason for this is the importance of light dosimetry. When using a forward-projecting fiber or a bulbous tip spherical distribution fiber, the dosimetry depends on certain assumptions that may or may not be true. For example, when using a forward-projecting fiber, the power output per square centimeter depends on the area illuminated. For a fixed-power output, the power per square centimeter decreases as the area illuminated increases. Although the area illuminated can be accurately measured when treating skin metastases to the chest wall, this cannot be done within the airway. Thus, although the power going to the fiber can be controlled, the power per square centimeter cannot. Thus, control of dosimetry may be adversely affected. Whether this influences outcomes is unclear but is discussed below in the section on clinical studies.

When using a cylindrical light-diffusing fiber, a power of 400 mW/cm is typically used, with a total energy delivery of 200 to 300 J/cm. Typically, 200 J/cm is used for carcinoma in situ, while up to 300 J/cm is used for more advanced disease. Of the cylindrical fibers currently available for use with the bronchoscope, the 1- and 2.5-cm fibers are the most useful and are commercially available. Thus, the initial laser bronchoscopy procedure consists of simply placing a nonthermal laser either within or adjacent to the tumor for 500 to 750 seconds. Tumor necrosis will then take place over the next 24 to 48 hours.

Removal of Necrotic Debris

Between 24 and 48 hours after the initial laser treatment, the tumor becomes necrotic. Also, depending on the size of the tumor and the ability of the patient to cough, the necrotic debris will obstruct the airway. At this time, therefore, repeat bronchoscopy is needed for pulmonary hygiene. If residual tumor is present after removal of necrotic debris, repeat laser treatment can be done. If additional laser treatment is given, repeat pulmonary hygiene bronchoscopy is mandatory 24 to 48 hours later. Aggressive debridement of all necrotic debris is critical since it will absorb light and limit the efficacy of any further laser treatments, in addition to leading to atelectasis and respiratory compromise.

The tumor at this stage is very avascular and will appear white if PDT has been successful. It will
have the consistency of very thick mucus and will be somewhat gelatinous in nature (Figure 1). As predicted based on the mechanism of injury (see above), virtually no bleeding occurs with mechanical debridement if PDT has been successful.

**Clinical Studies**

Potential clinical applications of photosensitizers include early diagnosis and localization of lung cancer, treatment of carcinoma in situ, and treatment of advanced endobronchial disease from both primary and metastatic tumors. The diagnostic use of photosensitizers is based on changes in the fluorescence spectrum of tumor tissue as compared to normal tissue. The hematoporphyrins have been shown to successfully localize radiographically and bronchoscopically occult tumors.[43-45] Fluorescence bronchoscopy uses this same principle without any photosensitizer to try to localize tumors. The diagnostic applications of photosensitizers and fluorescence bronchoscopy systems have been reviewed elsewhere. For the purposes of this review, we will focus on PDT as a therapeutic tool. Primary attention will be given to clinical studies relevant to the current use of PDT in clinical practice rather than in a research setting. Current clinical applications of PDT include carcinoma in situ and advanced endobronchial disease.

**Carcinoma in Situ**

Carcinoma in situ represents one clinical scenario in which PDT may be particularly applicable. The relatively noninvasive nature of the procedure, combined with its selective tumor destruction, the preservation of lung function, and the ability to repeat treatments in a group of patients at risk for second primary tumors, make it intuitively appealing. Analysis of the literature on PDT in early-stage lung cancer needs to take into consideration a variety of factors, including variations in case-finding methods, photosensitizing agents, light dosimetry, and outcome measures (Table 1). Many studies of PDT in carcinoma in situ include patients with early-stage carcinoma who were at high risk for surgical intervention. Thus, the definition of carcinoma in situ in some of these studies actually includes stage IA tumors, which are more advanced than carcinoma in situ and presumably have a worse prognosis. Thus, [true] carcinoma in situ may actually have a better prognosis than represented in these studies. However, distinguishing true carcinoma in situ from early-stage IA disease may be difficult. Importantly, case finding and outcomes differ in the various studies, and the photosensitizing agents and light dosimetry vary significantly.

Given these limitations, several important conclusions can be drawn. First, despite the variability in study design, methods, and outcome measures, the results are fairly consistent, with local complete and partial remission rates of 70% to 100% (Table 1).[46-50] In a study by Edell and Cortese, 14 early-stage cancers were treated, 2 to 4 days after infusion of a hematoporphyrin derivative, using a light dosimetry of 200 to 400 J/cm² at 630 nm.[46] At a follow-up of 7 to 49 months, 77% of the tumors demonstrated no recurrence. Similarly, in a study by Kato et al involving 95 tumors, the complete response rate was 94.2% for lesions with a longitudinal length of less than 1.0 cm but decreased to 37.5% for tumors with a length of more than 2 cm.[47] The 5-year survival rate in this study was 68.4% by Kaplan-Meier analysis. Furuse et al demonstrated similar findings in a series of 64 tumors treated with porfimer sodium.[48] Again, tumors with a length of less than 1 cm had a higher complete response rate (98.7%) than tumors longer than 1 cm (42.9%).

**Predictors of PDT Success or Failure**

Thus, it appears that an important predictor of the utility of PDT as a viable alternative for [early-stage] disease is relatively small tumor size. Certainly, patients with carcinoma in situ (as detected by fluorescence bronchoscopy) would be logical candidates for this modality. In the setting of early-stage disease but not true carcinoma in situ, PDT may still be an option in carefully selected patients who have a smaller, central, squamous cell carcinoma and have high surgical risk or other comorbidities.[49,50] The role in this setting of the combination of PDT with other modalities, such as radiation, chemotherapy, and brachytherapy, has not been fully defined.

Other factors that have been associated with treatment failures include tumor distal to segmental bronchial bifurcations, bronchial stump tumors, and underestimation of the true tumor size. In an analysis of 23 patients with intraluminal stage I lung cancer, Sutejda et al demonstrated frequent treatment failures with distal segmental tumors or stump recurrences and attributed this to insufficient dosimetry and, possibly, the inability of the light to penetrate the bronchial stump to an adequate depth.[49] An animal study evaluating light dosimetry in porcine tracheas supported this...
theory, demonstrating significant variations in light dosimetry using this model.[51] Similarly, Hayata et al found that PDT was also less effective in achieving a complete response when the tumor extended beyond the cartilaginous layer.[52] Since it had been shown previously that only 68% of radiologically occult lung cancers were truly confined to the cartilaginous layer, the finding of significant recurrence rates is consistent with these previous studies.[53] More accurate preoperative assessment is needed, possibly with fluorescence bronchoscopy and endobronchial ultrasound. These techniques may help in identifying patients with unrecognized extension of their disease or those with residual tumor.

**Side Effect Profile** Importantly, in all of the studies of PDT for early-stage disease, the side effect profile has been very favorable. Adverse reactions in this lower-risk group (as compared to patients with advanced unresectable lung cancer) predominantly include mild sunburn-type reactions. In many of these studies, patients with remarkably low Karnofsky performance scores (< 40) and multiple other comorbidities have successfully undergone PDT. Thus, from a side effect and safety perspective, PDT certainly has advantages as a treatment for carcinoma in situ.

**Unresolved Issues** Of course, for PDT to have a significant impact in early-stage disease requires that there be a cost-effective method for screening and localizing disease. Importantly, not all early-stage carcinomas may be equally amenable to PDT, and the efficacy of PDT may differ according to the type of tumor, location, and method of screening. Much of the work with carcinoma in situ and early-stage tumors has been conducted in patients in whom squamous cell carcinoma was the predominant cell type. The incidence of occult lymph node metastases in these patients is low to nonexistent when tumors are less than 2 cm.[54] This suggests that a bronchoscopic type of treatment may be appropriate in some cases. Occult lymph node metastasis is more common with adenocarcinoma, however. Does this mean that PDT would be less effective if carcinoma in situ with features of adenocarcinoma were identified? Would this difference be of sufficient clinical significance to warrant a different treatment approach? The answers to these questions remain unknown given the level of evidence currently available. Whether or not current recommendations will remain valid when applied to other populations with a higher incidence of adenocarcinoma using different case-finding methods and with different tumor locations (ie, more peripheral lesions), remains unclear. However, even if PDT were effective only for early-stage squamous cell carcinoma, this would represent a significant advance, but only if there were a feasible way to identify these patients at an early stage. Thus, any evaluation of the efficacy of PDT for carcinoma in situ must take into account case-finding methodology, tumor type, tumor location, and treatment alternatives.

**Advanced Endobronchial Tumors** Photodynamic therapy has also been evaluated as a potential tool for the treatment of patients with unresectable lung cancer and advanced endobronchial disease (Figure 2). Since there is currently no method in widespread clinical use for early detection or cancer localization, this population represents a far larger group of patients than the carcinoma in situ group. The standard of therapy for advanced endobronchial disease currently is neodymium:yttrium-aluminum garnet (Nd-YAG) laser resection. Other alternatives include radiation therapy, brachytherapy, cryotherapy, and electrocautery. Most of the data on PDT come from case series. Reports on the efficacy of PDT in this arena, therefore, are difficult to compare to results with other modalities.

In a large, prospective series of 100 patients with advanced inoperable stage IIIA-IV bronchogenic cancer with endobronchial obstruction, PDT resulted in significant improvements in endobronchial obstruction, pulmonary function testing, and palliation of symptoms.[55] The mean percentage of endoluminal obstruction fell from 85.8% to 17.5%, along with improvements in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) of 430 mL and 280 mL, respectively. In another series by McCaughan in patients with advanced primary lung cancer, the mean percentage of endobronchial obstruction fell from 84% prior to PDT to 18% four weeks later.[56] Thus, there is limited evidence that PDT can perform well for palliation of advanced endobronchial obstruction.

**DT vs Other Modalities** In a study by Lam et al of PDT combined with radiotherapy vs radiotherapy alone in 41 patients with advanced endobronchial obstruction, PDT plus radiation therapy was dramatically better than radiation alone.[57] Only 10% of patients had a complete reopening of the airway with radiotherapy alone, as compared with 70% of those treated with the combination.

In a prospective comparison of PDT vs Nd-YAG laser therapy in 26 patients with stage III inoperable lung cancer, Moghissi et al demonstrated better results with PDT.[58] The median percentage of
obstruction was similar in the two groups prior to treatment (83.4% in the Nd-YAG group vs 88.7% in the PDT group). However, after 1 month, the post-treatment percentage of obstruction was significantly lower in the PDT group than in the Nd-YAG group (17% vs 39.1%). Photodynamic therapy also produced significantly greater improvements in FEV$_1$ and FVC.

In another prospective, randomized trial of PDT vs Nd-YAG laser therapy in 211 patients with partially obstructive lung cancer conducted in 35 centers in Europe and the United States, response rates were similar at 1 week. By 1 month, however, response rates were higher in the PDT group than in the Nd-YAG group in both Europe (61% vs 36%) and the United States (42% vs 19%). Moreover, complete response rates (based on biopsy proven results) were also superior in the PDT groups than in the Nd-YAG groups (Europe: 12% vs 3%; United States: 6% vs 5%). Side effects and adverse reactions were similar in both groups, with the exception of an increase in skin photosensitivity in the PDT group.

**Summary** Although only limited data are available, PDT seems to have comparable efficacy to the Nd-YAG laser and is superior to radiation therapy alone. Advantages of PDT include the technical ease of the procedure; greater margin for error, especially in smaller bronchi; less risk of bronchial perforation; decreased risk of intraoperative hemorrhage; and, perhaps, longer duration of response. This longer response duration may be secondary to destruction of invisible submucosal tumor that is missed with the Nd-YAG laser.

Importantly, PDT does have significant limitations in the treatment for advanced endobronchial disease. These include its extremely high cost ($5,000 per patient for the photosensitizer alone), the need for repeat pulmonary toilet bronchoscopies, and the inconvenience to the patient caused by skin photosensitivity.

In addition, PDT is primarily effective for endobronchial tumors and is not effective for obstruction caused by extrinsic compression or submucosal spread (Figure 3). However, Nd-YAG, cryotherapy, and electrocautery are not effective interventions for these problems either. Airway stenting is probably the treatment of choice in these situations.

Also, PDT is much slower than the Nd-YAG laser. In patients with acute respiratory compromise, one Nd-YAG laser treatment can achieve relief of dyspnea. The use of PDT for acute respiratory distress or for ventilated patients has not been reported.

Furthermore, based on our experience, we do not use PDT when there is significant tracheal stenosis. In this situation, the concern is that the significant tumor necrosis and mucus plugging caused by PDT may result in sudden airway occlusion and respiratory failure. Thus, in the setting of endotracheal obstruction, based only on anecdotal evidence, Nd-YAG laser therapy is preferable.

Finally, although it is clear that for carcinoma in situ, PDT can be performed via the flexible bronchoscope, it remains unclear whether patients with more advanced disease can be effectively treated with flexible bronchoscopy. Many of the early studies used rigid bronchoscopy. Similarly, in a recent large prospective case series by Moghissi et al in patients with advanced endobronchial disease, all of the patients underwent PDT with rigid bronchoscopy under general anesthesia. Further clarification of this issue is important, considering that most US pulmonologists do not routinely perform rigid bronchoscopy.

**Role of PDT in a Multimodality Approach**

Photodynamic therapy is a promising approach that may complement other therapeutic modalities in several clinical scenarios, such as problems related to carcinoma in situ and endobronchial tumors in patients with advanced disease. In each of these cases, the effectiveness of PDT and its appropriate use need to be considered in the context of a multimodality treatment approach.

**Carcinoma in Situ**

With respect to carcinoma in situ, the appropriateness of PDT depends on having a case-finding method available that identifies patients early enough to be treated with this modality. Certainly, any patient with good cardiopulmonary function should be considered for surgery. However, in many cases, other comorbidities, such as chronic obstructive lung disease, may preclude surgery.

For PDT to be effectively utilized in these cases will require more than just a screening method. It will be necessary to identify patients at high risk for occult lymph node metastases, in whom surgery, even if it entails greater risk, may be warranted. Therefore, the diagnostic approach will have to take into account the treatment options available to that patient.

Concurrent chemotherapy or radiation therapy may be beneficial in high-risk patients, but no data are yet available to indicate the optimal combination of therapies in these patients. In a study by Cortese et al in patients with early-stage squamous cell carcinomas, PDT used in a multimodality approach was associated with improved outcomes compared to chemotherapy alone.

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treatment approach allowed 43% of patients to be spared an operation.[50]

**Advanced Endobronchial Disease**

In the case of advanced endobronchial disease, PDT is useful in treating endobronchial tumors that are causing clinically significant dyspnea or are likely to progress and lead to further clinical complications, such as postobstructive pneumonia. Two issues become important in utilizing PDT in these settings: (1) careful patient selection, and (2) the combination of PDT with appropriate radiation and chemotherapy.

**Patient Selection**—Since treatment with PDT in these cases is purely palliative, only lesions in the larger airway should be treated. If a patient with metastatic disease has a small lesion that is visible in a subsegmental airway but is not causing symptoms, it is not worth treating. Similarly, in patients with no viable lung distal to the obstruction, PDT is not warranted.

A useful way to frame the clinical question is to ask whether or not removal of this localized obstruction would result in a meaningful change in the patient’s symptoms, quality of life, or later risk of complications. When approaching these complicated patients, it is important to combine PDT with other interventional tools, such as airway stents, Nd-YAG laser therapy, and cryotherapy. Each tool will have its own specific role, depending on the problem, and multiple tools will be needed in many cases. For example, for a patient who has endobronchial obstruction with concurrent extrinsic compression, a combined approach using PDT with stenting may be best, as either tool alone will be ineffective.

**Integrating PDT With Radiation and Chemotherapy**—Although it appears that PDT plus radiotherapy is superior to radiotherapy alone, the optimal sequencing of these modalities has yet to be refined. Similarly, to date, PDT has shown remarkably few interactions with other chemotherapeutic agents. Theoretical concerns have been raised about the possibility of interactions with agents that may generate additional or cumulative free radical injury, but whether this leads to a clinically significant increase in complications is unclear. Based on the large number of patients treated with PDT combined with chemotherapy to date, no clear trend has been demonstrated. Our approach has been to use endobronchial interventions initially to avoid having a situation in which a patient develops a postobstructive pneumonia while receiving chemotherapy and having pancytopenia. Any laser intervention at that point would pose too high a risk.

Similarly, based on anecdotal data, we initiate laser interventions, whether PDT or Nd-YAG, prior to radiation if possible, since the amount of time to restore a patent airway and reduce the risk of postobstructive pneumonia is shortened. In addition, by relieving airway obstruction, patients have improved pulmonary reserve and are better able to tolerate other complications, such as pneumonia and radiation pneumonitis.

Based on these considerations, it is clear that for PDT to be optimally effective, a team approach for integrating PDT into a multimodality treatment program is necessary. The optimum sequencing of these modalities requires further study but will always need to be individualized for each patient.

**Summary**

Photodynamic therapy utilizes photosensitizing agents that are selectively retained by tumors. These agents achieve high tumor-tissue concentrations but are inactive by themselves. When activated by light, photosensitizers generate free radicals, resulting in membrane injury, vascular injury, and immune-mediated injury with relatively selective cytotoxicity to tumor cells. Clinically, PDT can be used to treat in situ lung cancer, as well as more advanced lung tumors with endobronchial obstruction. Photodynamic therapy should be viewed as one of many tools that can be used to manage airway problems in patients with lung cancer. Often, it will need to be used in conjunction with other techniques, such as airway stenting, Nd-YAG laser therapy, or cryotherapy. For PDT to be effective, it must be integrated into a multimodality approach that includes chemotherapy and radiation therapy.

**References:**


22. Hilf R, Smail DB, Murant RS: Hematoporphyrin derivative-induced photosensitivity of mitochondrial succinate dehydrogenase and selected cytosolic enzymes of R3230AC mammary


