Application of Photodynamic Therapy to Lung Cancer Treatment

Aladin Milutinovic

May 3, 2007

Tufts University
BME 101: Biomedical Optics
Spring 2007

Outline

A. Introduction

A new technology for treatment of cancer that is being explored is Photodynamic Therapy (PDT). In PDT, chemicals known as photosensistizers (PS) are localized into cancerous tissues. Shining laser light onto the tissues causes the photosensitizer to generate reactive oxygen species within the tissue. The reactive oxygen attacks the cell organelles and disrupts regular cell function, which leads to cell death. Targeting the photosensitizer to cancerous tissue determines which cells will die under light exposure. As you can imagine, there are many challenges to achieving PS specificity in order not to harm healthy tissues. Nevertheless, there are several FDA approved photosensitizers and applications of PDT to treating various cancers. One of the cancers that this paper will focus on is lung cancer.[4]

There are over 150,000 deaths related to lung cancer in United States every year.[3] In many cases the lung cancer is inoperable due to patient inability to withstand a surgery and locating of the cancer. PDT has been used in many instances of inoperable lung cancer with reduced mortality. In this paper, we will elucidate some of the basic principles of PDT, examine the instrumentation and applications that are involved, and speculate on future possibilities and research related to PDT.

B. PDT Background

Photodynamic Therapy (PDT) as mentioned above works on three basic principles: light, photosensitizer, and oxygen. These elements work together to determine selectivity of PDT to killing cells that are cancerous. In order to understand how light interacts with photosensitizers to create radical oxygen species, we must look into the physics behind these photochemical reactions.[6]

B.1. Photochemistry Physics

Quantum mechanics explains how light interaction with chemicals causes chemical reactions to occur. The driving force for the chemical interactions is the energy delivered from the light photons that is converted into chemical vibrations. Figure 1 shows a simplified energy diagram of light interaction with photosensitizer to create radical oxygen species.[6]

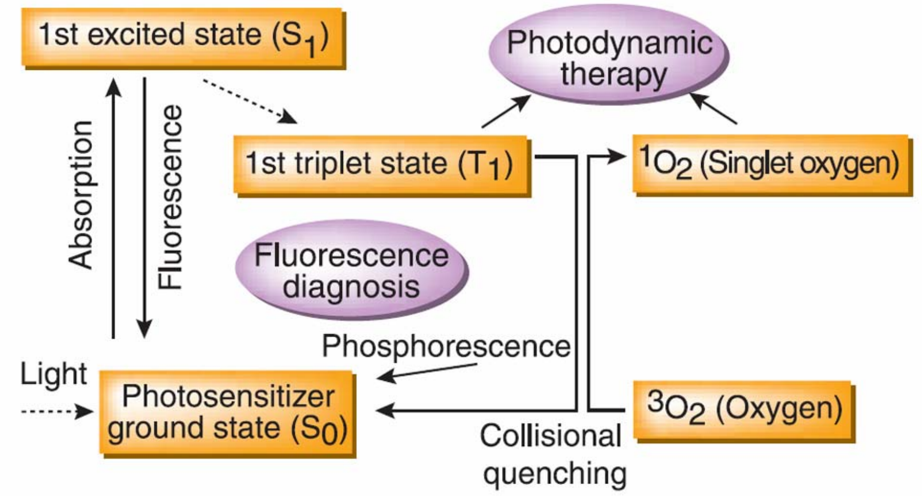


Figure 1. Energy diagram depicting PDT. Laser light excites the photosensitizer (PS) to a higher energy state. The PS causes generation of reactive oxygen species that is toxic to the cells.[6]

Illumination by laser light at a specific wavelength that corresponds to the photosensitizer absorption spectrum determines how efficiently PS gets excited from S_0 to S_1. At S_1, the PS can either decay back to S_0 and cause fluorescence or decay into a lower vibrational energy triplet state T_1. The lifetime at T_1 is much longer than at S_1, and is believed that most of the interaction that causes generation of toxicity comes from molecules that are in T_1 state. From T_1, the molecule can either relax back to S_0 or interact with molecules such as oxygen to create toxic species and return to its low state S_0 (collisional quenching). The fluorescence and phosphorescence is being explored as a way to detect where the tumors are located since the fluorescing regions can be visualized with microscopy.[4,6]

There are two ways that T_1 state can cause cell damage: direct interaction of T_1 state to generate free radicals, or generation of reactive oxygen species. The PS at T_1 energy level can excite other molecules to cause toxicity; however, it is believed that generation of singlet oxygen is the dominant mechanism. Both PS at T_1 energy level and singlet oxygen $^1O_2$ are the active molecules that are the killing force in PDT.[6]

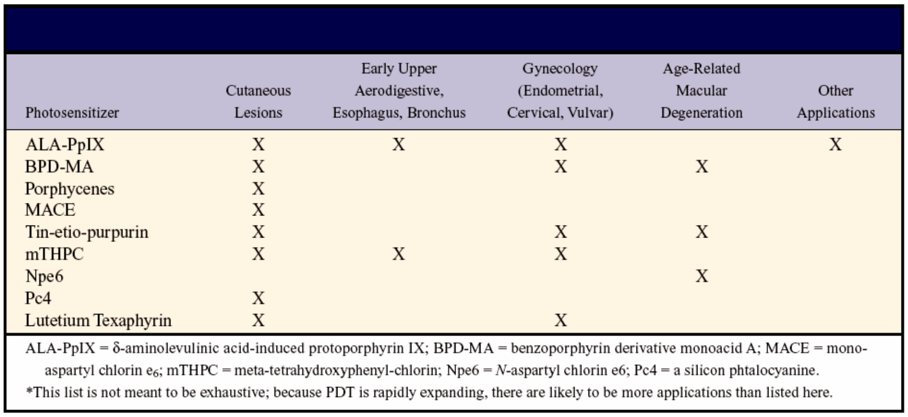
B.2. Photosensitizers and Phototoxicity

There are many photosensitizers being explored today. Several important ones are currently FDA approved and used for treatment of various cancers. The three major photosensitizers are Photofrin (porfimer sodium, PF), 5-aminolaevulanic acid (ALA), and Verteporfin (benzoporphyrin derivative, BPD).[1,6]

One important property of the photosensitizer is its localization profile. We prefer photosensitizers that localize into cell membranes, but do not want it to localize into cell nuclei. For this reason, only non-mutagenic photosensitizers are applicable to PDT. Preferably, the photosensitizer should localize in cancerous tissue. However, it is difficult to control where PS ends up when introduced systemically. In order to achieve a level of selectivity, the laser light source can be used to illuminate only the regions of interest (cells that are cancerous) without harming other healthy tissue. There is one exception, and that is in the brain; PS tends to concentrate much more into tumor tissue then in the rest of the brain.[1]

The first generation photosensitizer like Photofrin are available for PDT of tumors that are near the surface of the tissue. The absorption peak is at 630nm, which is highly absorbed by tissues. Therefore, the maximum depth for therapy is only about half of a centimeter. Its residency in tissues is on the order of weeks, which is not ideal. The long residency leaves the patients sensitive to light. This PS has found applications in various carcinomas that are near the surface of tissues, such as in early state lung cancer, stomach, cervix, and bladder cancers.[1]

The second generation of photosensitizers are designed such that they have low residency lifetime in tissues and are activated at larger wavelengths. Larger wavelengths ($\lambda > 650$nm and into Near Infrared) have less absorption in tissues, and thus can penetrate deeper into tissue.[1] The PS molar absorption coefficient has to be increased in order to increase the quantum yield. Increasing the molar absorption coefficient increases the effectiveness of the PS to absorb light. Increased effectiveness of PS means that smaller concentrations of PS are needed to conduct therapy, the amount of time for therapy is less, and thus the lifetime of PS can be decreased. All these parameters factor into the current design of photosensitizers. Table 1 shows a partial list of photosensitizers currently being investigated.



Photosensitizer	Cutaneous Lesions	Early Upper Aerodigestive, Esophagus, Bronchus	Gynecology (Endometrial, Cervical, Vulvar)	Age-Related Macular Degeneration	Other Applications
ALA-PpIX	X	X	X		X
BPD-MA	X		X	X	
Porphycenes	X				
MACE	X				
Tin-etio-purpurin	X		X	X	
mTHPC	X	X	X		
Npe6				X	
Pc4	X				
Lutetium Texaphyrin	X		X		

ALA-PpIX = δ-aminolevulinic acid-induced protoporphyrin IX; BPD-MA = benzoporphyrin derivative monoacid A; MACE = mono-aspartyl chlorin e_6; mTHPC = meta-tetrahydroxyphenyl-chlorin; Npe6 = *N*-aspartyl chlorin e6; Pc4 = a silicon phtalocyanine.

*This list is not meant to be exhaustive; because PDT is rapidly expanding, there are likely to be more applications than listed here.

Table 1. Several second generation photosensitizers in experiementation or clinical trials.[6]

B.3. Dosimetry

The amount of light that is required for PDT to work is referred to as light dosimetry. Getting the right amount of light into the region of interest is a critical component of PDT. If too much light is given, ulcerations, perforations and strictures can result. On the other hand, if not enough light is delivered, the therapy is not successful at killing the whole tumor.

Similarly, dosimetry of photosensitizer is just as critical as dosimetry of light. Getting the right concentration of photosensitizer in the tissue determines the effectiveness of PDT. The effects are similar to that of light dosimetry mismatch: if not enough PS is present, the therapy fails, and if too much PS is present, ulcerations, perforations and strictures result in the tissues.[6]

Photobleaching phenomena of PS is an important component that plays a role in dosimetry. Over time, PS degrades as it reacts with various chemicals. The breakdown of PS results in loss of its ability to absorb light and create singlet oxygen. This effect is referred to as photobleaching. Photobleaching also has to be calculated in with PS dosimetry in order for the therapy to be effective, especially with second generation photosensitizers that have short lifetime *in vivo*.[6]

C. Lung Cancer

One application of PDT is in treatment of lung carcinomas. Over 150,000 people die from inoperable lung cancer every year in the United States.[3] This statistic indicates a significant clinical need for treating lung tumors. One of the very first PDT treatments approved is Photofrin (porfimer sodium) photosensitizer. In the early 1990's in several countries (USA, Canada, Japan, and few European) Photofrin was approved for various cancers, of which lung cancer is one of them.[2]

Another photosensitizer that is being used to treat lung cancer is mono-L-aspartyl chlorine e6 (talaporfin sodium, Laserphyrin, NPe6). It was approved in Japan in 2003. This second generation PS has an absorption peak at 664nm, reduced systemic lifetime, reduced photosensitivity, and can be administered intravenously with 4 hours of exposure time.

The photosensitizers mentioned here are usable only with early-stage lung cancers. In United States, these cancers are characterized as stage 0 and stage 1. The tumor must be located in bronchi that are no smaller than 2cm in diameter, non invasive, and located within the bronchial wall. These requirements limit the applicability of bronchoscopic intervention with PDT.[2]

D. Instrumentation

The instrumentation that is involved in PDT varies depending on the location of cancer that needs to be treated. For lung cancers, a bronchoscope is used. A laser source is threaded through the bronchoscope with fiberoptic cables.

In Japan, for Photofrin PS, an excimer dye laser EDO or a YAG-OPO laser source are used. These lasers produce light at 630nm wavelength. The light is transmitted through a quartz fiber through a bronchoscope channel. In other countries, diode lasers are used. Using these systems and Photofrin, the illumination time is generally 10 to 40 minutes at 100 to 800 J/cm^2 (4 mJ/pulse, 20 to 60 Hz) after 24 to 48 hours of injecting PS.[2]

For photosensitizer NPe6, an aluminum gallium indium phosphorus (AlGaInP) diode laser is used. It is tunable to the 664nm wavelength to maximize absorption. Its power can be varied from 50-500nW and is portable weighing only 20kg.[2] Portability is an important factor for making PDT a possibility for treating cancer inexpensively across many geographic locations.

An alternative way to administer light into tumors that are inaccessible and large is to use a grid of needles threaded with optical fibers. Figure 2 shows a schematic of a system that allows interstitial delivery of light for PDT. For example, 19 gauge needles arranged in an equidistant fashion are threaded with optical fibers to deliver light from a laser source. The needles have to be spaced evenly in order to ensure that a constant distribution of light is delivered to the tumor area. With image guidance (ultrasound or x-ray), the needles can be positioned into the tumor area. By pulling the needles out layer-by-layer and exposing each layer with light for a given amount of time, a large area can be illuminated.[1]

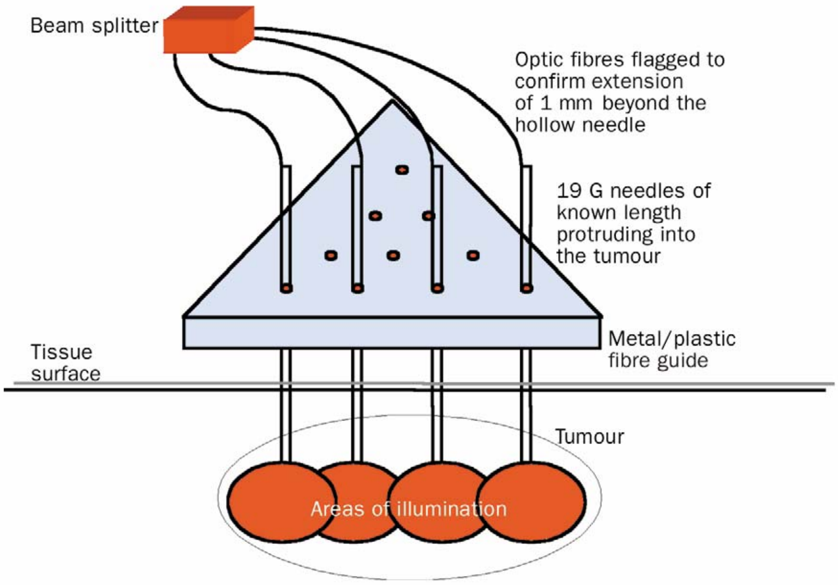


Figure 2. Interstitian light delivery using equidistant 19G needles threaded with optical fibers.[1]

E. PDT Methods for Lung Cancer

There are several methods for Photodynamic Therapy of lung cancers, which vary depending on the stage at which the cancer is detected and its location and size. We will cover several examples in the next sections.

E.1. PDT for Early-Stage Central Lung Cancers

In the early stage lung cancers, typical symptoms are increased mucus and blood in mucus. These cancers are classified as stage 0 and stage 1 by US National Cancer Institute. The cancers at the moment are not invasive and are located in a small region accessible with a bronchoscope. Several studies at various medical centers and countries showed that PDT is a good alternative to surgery for early-stage central lung cancers. For example, a study in Japan using Photofrin (2mg/kg) and 100 to 200 J/cm^2 illumination with 630nm source showed an 85% complete response of tumor to PDT. In another phase II clinical trial, Laserphyrin (40mg/kg) was used with 100J/cm^2 illumination over 4 hours causing an 87% complete response in the study population.[2,5]

E.2. PDT for Peripheral Lung Cancers

In peripheral lung cancers, a needle is used to probe into the tumor area. An optical fiber is threaded through the needle to deliver light. The needle is guided into place by CT. A diffuse fiber can then be inserted into the tumor area that has a 2cm long tip.[2] Alternatively, light can be delivered using a system that is similar procedure is illustrated in Figure 2 using a network of needles to illuminate a larger tumor.[1]

E.3. PDT for Advanced Lung Cancers

In advanced lung cancer, the airways are obstructed by the tumor. PDT has been shown to work with 75% success rate. However, an alternative method using laser resection is more successful with an 85% success rate. However, it was found that PDT was more effective at treating lobar and segmental bronchi.[2]

E.4. Preoperative PDT

PDT has been used with patients that will be undergoing resection surgery. The reason for using PDT is to reduce the tumor as much as possible. As a result, the surgeon does not have to remove more than the area that is necessary for removal. Three to nine weeks after administration of PDT, some of the patients with inoperable tumors healed enough that the remaining tumor could be removed while preserving enough lung function to sustain life.[2]

F. Advantages and Disadvantages of PDT

There are many advantages and several disadvantages to Photodynamic Therapy. The advantages indicate that there is great potential for PDT with the design of better photosensitizers.

F.1. Advantages of PDT

PDT is a very powerful method for treating many inoperable cancers. The simplicity of PDT is a great advantage. Using light and a photosensitizer, a surgen can selectively illuminate the tissue that he sees to be cancerous. The repeatability of PDT is another great advantage. The therapy can be repeated many times in order to kill returning tumors. When we compare PDT with other cancer treatment techniques such as chemotherapy and surgery, there is decreased morbidity due to fewer complications and decreased systemic toxicity. As a result of PDT, function is restored without adverse cosmetic effects that surgery and chemotherapy can leave behind. As the laser technology develops and becomes cheaper, PDT will be much less expensive and portable treatment. Overall, these advantages indicate the great potential for PDT.

F.2. Disadvantages of PDT

With all the advantages that we just indicated above, there are several challenges to designing an effective photodynamic therapy. The major challenge is in the selectivity and design of photosensitizers. Ideally we do not want PS to cause damage to healthy tissue. The risk of damage is reduced by selectively positioning the laser source; however, it is difficult to avoid illuminating healthy nearby tissue.

Another major problem with PDT is skin photosensitivity that results with administration of the photosensitizer. For example, skin photosensitivity can last

4-6 weeks after administering Photofrin. Increasing PS clearance rate and reactivity is a problem that needs to be addressed.

With PDT, nearby tissue damage is possible. Ulcerations, perforations, and strictures can result if dosimetry is not carefully calculated. The dosimetry has to be accurately calculated and carried out during therapy in order to cause tumor damage without inflicting serious damage to surrounding tissues.

With the prospective of cheaper lasers, PDT would be an inexpensive provedure. However, currently the lasers that are used for PDT are expensive tunable lasers. As a result, PDT is not as widely used today.

There is also decreased effectiveness of PDT with advanced lung cancers where large tumors need to be illuminated. With large tumors, dosimetry calculations are much more complicated. Many variables and differences in tissue density can cause uneven distribution of laser light. These variables can cause inconsistent illumination and photosensitizer localization, which may lead to incomplete treatment.

G. Suggested Improvements

Even though there are still many challenges with PDT, the potential for success is large. In order to improve PDT, we have to examine and address the list of problems that are outlined in the above section F.2. The major challenges that are associated with PDT focus on photosensitizer design.

Photosensitizer design must take into account several factors: PS specificity for tumor tissue, lack of systemic toxicity, fast systemic clearance, and increased efficiency of converting light energy into reactive oxygen species. To improve PS design, the scientific research should focus on targeting PS to tumor cells. We have to understand if there are specific markers that tumor cells exhibit that we could take advantage for targeting. Recombinant DNA technology and immunology are fields that could provide us with answers to identify markers unique to tumor cells.

Another way to improve PDT is to take advantage of fluorescence signals that are emitted from the photosensitizer and phosphorescence signals from the creation of reactive oxygen species. The fluorescence and phosphorescence can provide visual instruction for the surgeon to maximize the removal of cancerous tissue without removing too much of the healthy tissue. These signals can be difficult to detect. Research and engineering is needed in order to determine the feasibility and validate the detection of these signals.

As PDT research advances and becomes more widely used with cheaper illumination lasers, it is a good and effective alternative to surgery and chemotherapy. Furthermore, combining PDT, surgery, and chemotherapy may cause even greater effectiveness of tumor suppression. PDT is a great example of an application of biomedical optics that has successfully been adapted from scientific research to clinical applications.

E. References

1. Colin Hopper. (2000). Photodynamic therapy: a clinical reality in the treatment of cancer. *Lancet Oncology*. **1**:212-219.

2. Jitsuo Usuda, et al. (2006). Photodynamic Therapy (PDT) for Lung Cancers. *Journal of Thoracic Oncology*. **1**(5):489-493.

3. Lung Cancer. (2007). Center for Disease Control Website. Retrieved on April 25, 2007: http://www.cdc.gov/cancer/lung/statistics/

4. Nicolas Solban, et al. (2006). Targeted Photodynamic Therapy. Lasers in Surgery and Medicine. **38**(5):522-531.

5. Patrick Ross Jr, et al. (2006). Incorporation of Photodynamic Therapy as an Induction Modality in Non-Small Cell Lung Cancer. *Lasers in Surgery and Medicine*. **38**(10):881–889.

6. Tayyaba Hasan, *et al*. (2003). Photodynamic Therapy of Cancer. Holland-Frei Cancer Medicine, 6th Edition, Chapter 35a.