Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2010 March 2; 7551: . doi:10.1117/12.843044.

A Treatment Planning System for Pleural PDT

Julia Sandell¹, Chang Chang¹, Jarod C. Finlay¹, and Timothy C. Zhu¹

Timothy C. Zhu: tzhu@mail.med.unenn.edu

¹Department of Radiation Oncology, School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

Abstract

Uniform light fluence distribution for patients undergoing photodynamic therapy (PDT) is critical to ensure predictable PDT outcome. However, common practice uses a point source to deliver light to the pleural cavity. To improve the uniformity of light fluence rate distribution, we have developed a treatment planning system using an infrared camera to track the movement of the point source. This study examines the light fluence (rate) delivered to chest phantom to simulate a patient undergoing pleural PDT. Fluence rate (mW/cm^2) and cumulative fluence (J/cm^2) was monitored at 7 different sites during the entire light treatment delivery. Isotropic detectors were used for in-vivo light dosimetry. Light fluence rate in the pleural cavity is also calculated using the diffusion approximation with a finite-element model. We have established a correlation between the light fluence rate distribution and the light fluence rate measured on the selected points based on a spherical cavity model. Integrating sphere theory is used to aid the calculation of light fluence rate on the surface of the sphere as well as inside tissue assuming uniform optical properties. The resulting treatment planning tool can be valuable as a clinical guideline for future pleural PDT treatment.

Keywords

Photodynamic therapy; light fluence; light dosimetry; intracavitary treatment planning

Introduction

Accurate dosimetry calculation in photodynamic therapy (PDT) is imperative in quantifying PDT treatment efficacy. In PDT, photosensitizer is administered to the site of the tumor. Illumination of the photosensitizer at a specific wavelength generates the highly toxic singlet oxygen which causes localized cell death and tissue necrosis. Efficacy of PDT therefore depends on the concentration of singlet oxygen, which in turn is determined by light fluence, photosensitizer concentration, and tissue oxygen level.[1] Direct measurement of singlet oxygen concentration is very difficult in vivo with large variability. As a result, to establish the correlation between the macroscopic treatment efficacy of PDT and the microscopic singlet oxygen concentration, one would need to rely on dosimetry calculation based on the

in vivo measurements of light fluence, photosensitizer concentration, and tissue oxygen level. [2] Accurate in vivo PDT dosimetry is imperative in understanding the mechanism of singlet oxygen's toxic effect and how this toxicity translates to tissue necrosis observed with PDT. Ultimately the goal of PDT dosimetry is to enable better PDT treatment planning based on optimized singlet oxygen distribution at the site of the tumor and as a result improve overall PDT treatment efficacy.

PDT is a local treatment, aptly suited to treat malignant, localized tumors such as those observed in malignant pleural mesothelioma (MPM).[3, 4] MPM has no standard treatment and the median survival for diagnosed patients is 6 to 17 months, depending on the disease stage. To treat MPM, PDT is coupled with surgical debulking of the tumorous tissue, part of a trend in multi-modal regimes to increase survival rates. The photosensitizer is administered to the patient, followed by a latent period referred to as the illumination time. After the illumination time is fulfilled, debulking surgery is performed, followed by illumination. In order to increase the success rate of such procedures, accurate dosimetry calculations are imperative to treatment efficacy. The proposed treatment plan presented here offers a method to improve real-time dosage application.

The pleural treatment program at Penn treats patients with MPM or pleural effusion. The photosensitizing drug, HPPH®, is administered 24-48 hours before irradiation. Once this illumination time is complete, the patient under goes surgical tumor debulking and irradiation. The irradiation is applied using a laser of wavelength 661 nm at 15- 60 J/cm². Within the thoracic cavity, the light delivery is continuously administered by a moving point source applied by the surgeon. It is at this point in the PDT treatment where real-time dosimetry becomes most critical. As the surgeon applies the light source, the knowledge of how well each particular area of the thoracic cavity is being irradiated will make the entire treatment process more effective and efficient.

2. Theory

2.1 Diffusion approximation

In order to create an accurate and efficient real-time fluence monitoring system we must compare our measurements to theoretical calculations of the fluence rate. The diffusion approximation is applied to a spherical geometry to model the cavities we hope to work with in a clinical setting. The diffusion approximation can be expressed as, [5]

$$-\nabla \cdot (D\nabla\phi) + \mu_a\phi = S \quad 1$$

where $D = \frac{1}{3(\mu_s' + \mu_s)}$ is the scattering coefficient (cm⁻²), μ_a is the absorption coefficient (cm⁻²), ϕ is the fluence rate, and S is the source term. Since we are working in spherical geometry, ϕ is a function of position r and independent of angle by symmetry. To solve for the fluence, we need to apply boundary conditions both within the medium surrounding the cavity and within the cavity,

$$\hat{n} \cdot \nabla \varphi = 0 \text{ (inside the turbid medium)} \quad 2$$

$$\varphi + A' D \hat{n} \cdot (\nabla \varphi) = 0 \text{ (inside cavity)} \quad 3$$

To solve for the fluence within the medium we assume that all back-scattered photons re-enter the medium. [6] Equations (1) – (3) are implemented in a commercial finite-element method (FEM) algorithm. (COMSOL, An analytical expression for the fluence rate for exists a point source in the center of a perfect sphere, [6]

$$\varphi(r) = \left[\frac{3S}{4\pi} \left\{ \frac{\mu_{tr} e^{-\mu_{eff}(r-r_0)}}{r(1+\mu_{eff}r_0)} - \frac{2}{3} \frac{e^{-\mu_t(r-r_0)}}{r^2} \right\} \right] \quad 4$$

where $\mu_{eff} = (3\mu_a\mu_{tr})^{1/2}$, $\mu_t = \mu_a + \mu_s$, $\mu_{tr} = \mu_a + \mu_s(1-g)$, and r_0 = cavity radius, and S is the power of the point source. This solution holds only for a centrally located, isotropic source.

2.2 Multiple Scattering and the boundary condition

When deriving this solution we assumed that the indices of refraction were matched between the cavity and surrounding medium. In reality, this assumption is unnecessary due to multiple scattering, which causes the fluence in the medium to be independent of whether the indices of refraction match. The boundary condition at the cavity-medium ($r_0=r$) does not change because the same total flux will reenter the medium over time. Within the cavity, a portion of the light from the source escapes and leaves the cavity, only to be scattered backward by the surrounding medium. Meanwhile, another portion of the light is scattered by the cavity wall. The reflected light within the cavity is described by, [7]

$$\varphi_r = \frac{\varphi_0}{1 - R_{12}} \quad 5$$

where φ_r is the reflected fluence rate, φ_0 is the initial fluence rate, and R_{12} is the diffuse reflectance. The fraction of light transmitted into the tissue is,

$$\varphi_t = \varphi_0 T \left(1 + R_{12} + R_{12}^2 + R_{12}^3 + \dots \right) = \frac{\varphi_0 T}{1 - R_{12}} = \varphi_0 \quad 6$$

where φ_t is the transmitted fluence rate, and φ_0 is the initial fluence before scattering. Equation 6 simplifies to 1 because the denominator equals the total direct fluence from the source. From this we see that the fluence entering and leaving the cavity remains constant, causing the fluence in the turbid medium to be independent of indices of refraction (Eq. 2). The fluence in the cavity, however, is affected by the presence of scattering material (Eq. 3).

2.3 Integrating Sphere

For an integrating sphere, the light fluence rate inside the sphere, assuming an infinite number of reflections, is uniform and can be calculated according to [8]:

$$\varphi_{sc} = \frac{4S}{A_s} \cdot \rho \cdot (1 + \rho(1-f) + \rho^2(1-f)^2 + \dots) = \frac{4S}{A_s} \cdot \frac{\rho}{1 - \rho(1-f)} \quad 7$$

where S is the light source power (mW), ρ is the diffuse reflectance of the scattering wall surface, $A_s (=4\pi R^2)$ is the total surface area with R the radius of the sphere, f is the fraction of the open surface area to the total surface area. Notice that this result assumes infinite number of scattering events on the wall before the light is detected.

One can also calculate the light fluence rate (ϕ) by including only the first, second, third scattering by using the summation up to the first, second, third terms, respectively, in middle term of Eq. (7). Equation (7) should be applicable for light fluence in pleural cavity since the integrating sphere theory does not restrict the shape of the enclosed reflective surface.

Considering the case of additional absorption from the non-scattering medium inside the pleural cavity (e.g., due to bleeding) and the direct light component, Eq. (7) can be modified to:

$$\varphi = \frac{S}{4\pi r^2} + \frac{4S}{A_s} \cdot \frac{\rho \cdot e^{-\mu_a r}}{1 - \rho(1-f)} \quad 8$$

where μ_a is the absorption coefficient of the non-scattering liquid and r is the distance to the point light source. The diffuse reflectance can be calculated based on the optical properties of the thoracic wall [9]:

$$\rho = \frac{a'}{2} \left(1 + e^{-(4/3)A \sqrt{3(1-a')}} \right) e^{-\sqrt{3(1-a')}} \quad 9$$

where $a' = \mu'_s / (\mu_a + \mu'_s)$ is the transport albedo, A , the internal reflection parameter is a function of the ratio of the index of refractions, $n_{rel} = n_t/n_v$: $A = (1+r_d)/(1-r_d)$, and

$r_d = -1.44n_{rel}^{-2} + 0.710n_{rel}^{-1} + 0.688 + 0.0636n_{rel}$. For water-tissue interface, A is 1.25 using $n_w = 1.33$ and $n_t = 1.4$.

3. Methods

3.1 Infrared camera

The infrared camera used in this study has an accuracy of 2 mm and data acquisition rate of 20-60 samples per second. The CCD itself is mounted on a stand set at a distance away from the sample that is to be measured (the sensors on the camera have a radius of 4 ft). A detector is placed on a wand is used to collect data from within the sample's cavity; this information is relayed to the CCD and stored. By moving the wand around in the cavity we are able to collect data about the geometry of the cavity. These data points are combined to make a 3D contour representation of the sample (See Fig. 1). These contour images are displayed in real-time, allowing observation of the geometry of the cavity as the data is being taken. This data is later used to provide real-time information on the location of the

light source and coupled with an empirical formula to calculate the light fluence, also in real-time.

3.2 Finite Element Model

A finite element model (FEM) was used to numerically calculate the fluence rate in a spherical cavity as a function of radial distance. The results of this model were used to verify the fluence rate calculated analytically. Boundary conditions, optical properties, geometry, and indices of refraction were all specified by the user to match the conditions of our analytical solution. The model was run with the light source located both centrally in the cavity and off-center to test the dependence of the fluence rate on source location.

4. Results

4.1 IR camera system

The IR camera system was able to be used to track the location of the light source in real-time. The camera detector was placed on a wand which doubled as a light source. Placed inside a phantom whose shape mimics that of a human pleural cavity, the detector relayed information to the CCD and, combined with the contours discussed previously, was able to show where the wand was located in the phantom (see Figure 2).

4.2 FEM versus diffusion approximation

Figure 4 shows the FEM results for a centrally located source (left) and a source located at 5 cm (right). The cavity radius and optical properties were $\mu_a = 0.3 \text{ cm}^{-1}$ and $\mu_s' = 14 \text{ cm}^{-1}$. We found the fluence rate inside the cavity to be independent of source location, which is to be expected in light of the effects of multiple scattering as discussed above.

Our analytical solution for the fluence rate was compared with the results of a FEM solution (see Figure 4). The two solutions agree very well except near the surface.

5. Discussion and Conclusion

The results presented here show promising aspects of pleural PDT treatment planning. The IR camera system developed here can potentially be used to obtain the location of the light-source position in real time. This tool would be an exciting addition to PDT treatment, to better help surgeons apply illumination more effectively as well as more efficiently. In future work we will implement the IR camera system in patients to obtain in-vivo data. Furthermore, we propose an empirical formula to calculate the fluence rate in a cavity in real time. By verifying our analytical solution with a FEM solution, we are able to assert that fluence rate is not dependent on index of refraction mismatch, angle, or source-location. Further work needs to be done to fully understand the fluence within the cavity as function of multiple scattering and attenuation. We plan to compare these results to phantom measurements in order to further verify our solution.

A marriage of the two results discussed here may provide a powerful tool to pleural treatment planning. By coupling real-time IR monitoring with our analytical fluence rate solution we hope to be able to develop a system which can display the fluence received in a

patient in real-time to the treatment team. This will provide an added dimension of efficiency to dosimetry in pleural PDT cases. This, in turn, may help increase the effectiveness and success rate of pleural PDT cases.

Acknowledgments

This work is supported by grant from National Institute of Health (NIH) P01 CA87971.

References

1. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbek M, Moan J, Peng Q. Photodynamic therapy. *Journal of the National Cancer Institute*. 1998; 90(12):889–905. [PubMed: 9637138]
2. Zhu TC, Finlay JC. The role of photodynamic therapy (PDT) physics. *Med Phys*. 2008; 35(7):3127–36. [PubMed: 18697538]
3. Pass HI, DeLaney TF, Tochner Z, Smith PE, Temeck BK, Pogrebniak HW, Kranda KC, Russo A, Friauf WS, Cole JW, et al. Intrapleural photodynamic therapy: results of a phase I trial. *Ann Surg Oncol*. 1991; 1(1):28–37. [PubMed: 7834425]
4. Pass HI, Tochner Z, DeLaney T, Smith P, Friauf W, Glatstein E, Travis W. Intraoperative photodynamic therapy for malignant mesothelioma. *Ann Thorac Surg*. 1990; 50(4):687–8. [PubMed: 2222072]
5. Star WM. Light dosimetry in vivo. *Phys Med Biol*. 1997; 42(5):763–87. [PubMed: 9172258]
6. Star WM. The relationship between integrating sphere and diffusion theory calculations of fluence rate at the wall of a spherical cavity. *Phys Med Biol*. 1995; 40:1–8. [PubMed: 7708833]
7. Haskell RC, Svaasand LO, Tsay TT, Feng TC, McAdams MS, Tromberg BJ. Boundary conditions for the diffusion equation in radiative transfer. *J Opt Soc Am A*. 1995; 11(10):2727–2741.
8. SphereOptics. 2007; 4 Integrating sphere design and application technical information.
9. Dimofte A, Zhu TC, Hahn SM, Lustig RA. In vivo light dosimetry for motexafin lutetium-mediated PDT of recurrent breast cancer. *Lasers Surg Med*. 2002; 31(5):305–12. [PubMed: 12430147]

Figure 1.
Formatted patient contour, upper (red) and lower (blue) inner surfaces from the IR camera.
Contours can then be read into Matlab and used to calculate the fluence rate in real-time.

Figure 2.
Demonstration of IR camera system. The white dot marks the location of the light source in the phantom.

Figure 3.

FEM solution for fluence rate with the light source located at the geometric center (left) and at 5 cm from the center (right). The radius of the cavity was 10 cm, $\mu_a = 0.3 \text{ cm}^{-1}$, $\mu_s' = 14 \text{ cm}^{-1}$.

Figure 4.

A comparison of fluence rate for FEM and analytical. solutions as a function of radial distance. Note how the Star (analytical) solution curves downward as the radial distance approaches zero while the FEM curve goes towards infinity.