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Real-time treatment light dose guidance of Pleural PDT: an update

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Abstract

The goal of this study was to develop and improve an infrared (IR) navigation system to deliver light dose uniformly during intracavitary PDT by tracking the movement of the light source and providing real-time feedback on the light fluence rate on the entire cavity surface area. In the current intrapleural PDT protocol, several detectors placed in selected locations in the pleural cavity monitor the light doses. To improve the delivery of light dose uniformity, an IR camera system is used to track the motion of the light source as well as the surface contour of the pleural cavity. Monte-Carlo simulation is used to improve the calculation algorithm for the effect of light that undergoes multiple scattering along the surface in addition to an improvement of the direct light calculation using an improved model that accounts for the anisotropy of the light from the light source.

Keywords

Photodynamic therapy; light fluence; light dosimetry; intra-cavitary treatment planning; MC simulation

INTRODUCTION

PDT is a local treatment aptly suitable to treat malignant, localized tumors such as those observed in malignant pleural mesothelioma (MPM).[1 – 3] 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 resection 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.

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After the illumination time is fulfilled, debulking surgery is performed, followed by illumination.

In order to increase the success rate of such procedures, accurate light dosimetry is imperative to treatment efficacy. We propose a novel method to guide the PDT treatment in order to achieve uniform distribution of light fluence. This novel method differs from the existing protocols in following aspects: 1) 4D (3D plus time) information of the treatment is obtained using this method by real-time updated unwrapped images; 2) The accumulative light fluence of every single point of the cavity surface being treated is displayed during the guidance, whereas the existing protocol displays light fluence information from a small number of locations.

The pleural treatment program at Penn treats patients with MPM or malignant pleural mesothelioma. Between 2010 and 2014, a Phase I HPPH-mediated PDT protocol was utilized for the IR navigation system. The photosensitizing drug, HPPH[®], is administered 24 – 48 hours before irradiation at a dosage of ~ 0.1 mg/kg (4 mg/m²) using 665 nm laser light at a light dose of 15 – 45 J/cm². After 2014, a Phase II Photofrin-mediated PDT protocol has been utilized for the IR navigation system. The photosensitizing drug, Photofrin[®], is administered 24 hours before irradiation at a dosage of 2 mg/kg using 630 nm laser light at a light dose of 60 J/cm². Within the thoracic cavity, the light delivery is continuously administered by a moving point source applied by radiation oncologist or the surgeon. It is at this point in the PDT treatment where real-time dosimetry guidance becomes most critical. As the light source is applied, 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 and can serve to better personalize treatment delivery.. This study is a progress report of our original IR navigation system for Pleural PDT. [4]

2. METHODS

2.1 Infrared tracking system

The Polaris[®] Spectra (North Digital Inc., Waterloo, Canada) system was used as the infrared (IR) camera to track treatment motion in 3D. Passive spherical markers (Fig. 1a) were used for the IR system to track the motion, and the accuracy of the system was ~0.5 mm in 3D. The maximum volume for the system was ~ 205 × 186 × 147 cm³, which was proper for operations on our patient population (Fig. 1b). Once the positioning wand was inside the working volume, the camera system started to track the position of the tip, on which point light source can be bonded. The position data were transferred to a computer using OpenIGTLink [5] at a rate of 20 – 60 Hz and can be displayed and processed by Matlab[®] (Mathworks, Natick, MA) in real time.

2.2 Treatment guidance procedure

The procedure of the image-guidance system for pleural PDT is described elsewhere [4, 6]. The treatment wand (Fig. 1a) was used in this procedure to complete the image guidance for taking treatment surface contour and for tracking the light source positions during PDT treatment. It was calibrated to locate its tip position by pivoting it around a fixed point (Fig. 1a). Then an optimization algorithm was used to determine the shift between the treatment

wand tip and the laser point source. [4] A separate wand with a steel tip was used to locate the detectors on the cavity surface, and also to determine the cavity contour. When the PDT treatment began using the treatment wand, the light fluence distribution on the cavity surface is calculated simultaneously so that the treatment can be guided by the real-time light fluence image to achieve a uniform light fluence on the cavity. To verify the image-guidance procedure, detectors were attached on the cavity surface so that the calculated light fluence can be compared with the measurements at multiple positions.

2.3 Light fluence calculation

One can calculate the light fluence rate (φ) by summing up the direct and the scattering light during pleural PDT. The direct light follows a simple formula for a point source, i.e.,

$$\varphi_{dir} = \frac{S}{4\pi r^2} A(\theta), \quad (1)$$

where r is the distance from the point of interest to the laser point source and $A(\theta)$ is the anisotropy correction function [7].

For a perfect integrating sphere, the scattered light fluence rate inside the sphere, assuming an infinite number of reflections, is uniform and can be calculated according to [4,8]:

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

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, and f is the fraction of the open surface area to the total surface area. The relationship between tissue optical properties and diffuse reflectance is given elsewhere [9]. Equation (2) is applicable for light fluence in the pleural cavity since the integrating sphere theory does not restrict the shape of the enclosed reflective surface. The validity of this equation for spheres with various radii is now verified using a Monte-Carlo (MC) simulation [10] for a range of tissue optical properties surrounding the sphere, inner medium type (air or water), location of the light source, and the addition of attenuation in the water medium inside the sphere (to simulate the effect of bleeding during PDT).

The light fluence during pleural PDT treatment was calculated on each point of the reconstructed surface contour, so that 4D (x, y, z, t) information on the contour surface is obtained. For visualization purposes, the 3D light fluence map at any particular time point was unwrapped into a 2D plane, so that the x-axis of the 2D mesh represents the azimuth angle, the y-axis of the 2D mesh represents the height (or z in 3D). This 2D light fluence mesh can be updated in real-time so that it can guide the PDT treatment for uniform light fluence distribution.

3. RESULTS

3.1 MC simulation of the scattered light inside a sphere surrounded by turbid medium

Figure 2 shows the fluence rate per power of a MC simulation in a sphere of radius $R_{\text{sph}} = 4$ cm using a collimated light source in the center (left plot) and an off-axis point of $0.5 R_{\text{sph}}$ (right plot) inside a water cavity. The tissue optical properties are: $\mu_a = 0.1, 0.5, 1 \text{ cm}^{-1}$ and $\mu_s' = 2, 10, 20 \text{ cm}^{-1}$. Figure 3 shows the fluence rate per power in what are otherwise the same condition as in Fig. 3 but with an added attenuation coefficient of 0.05 cm^{-1} inside the water cavity.

While the scattered light fluence rate per power is uniform, regardless of the location of source inside the water cavity (Fig. 2), it seems to be less uniform when there is significant attenuation inside the water cavity (Fig. 3b). However, this needs to be confirmed using MC with more incident photons (currently it is 2 million incident photons considered).

Figure 4 shows the scattered light fluence rate per power at 1 mm under tissue at the top edge of Figures 3 and 4, where the direct light is avoided, thus it is representative of scatter light fluence per power.

3.2 Image guidance results in patients

We have monitored the light source position during treatment for 20 patients from HPPH-mediated Pleural PDT [5] and 3 patients from Photofrin-mediated PDT. Light fluence for a Photofrin-mediated PDT patient is calculated on the pleural surface and unwrapped into a 2D color plot (Fig. 5). It is not possible yet to draw a definitive conclusion about the light fluence uniformity due to (1) uncertainty in pleural surface determination; (2) missing data of laser positioning due to obscuring of views of the reflective sphere to the IR camera; and (3) error in light fluence calculation due to missing scatter light calculation (which requires knowledge of tissue optical properties). However, even with these drawbacks, it is clear that physicians can use the map to guide the movement of laser source to achieve more uniform light fluence distribution.

4. DISCUSSION AND CONCLUSION

The results presented here show promising aspects of pleural PDT treatment planning. The IR camera system developed here is shown to be able to obtain the location of the light-source position in real time. This system would be a useful addition to PDT treatment to better help radiation oncologists and surgeons apply illumination more effectively and uniformly, which may lead to improved clinical outcomes for patients.

We have demonstrated that the IR camera system can be used in patients to obtain in-vivo data during pleural PDT. Furthermore, we verified the light fluence rate formula via MC simulations.

Among 23 patients from combined HPPH and Photofrin-mediated PDT, we obtained good data in 80% (16/23) patients. Among patients with good data, we can apply a correction introduced previously [4] in 75% (12/16) patients. Among patients with corrected light

fluence rate map, 90% (11/12) gets agreement between isotropic detector and calculation in all sites.

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Figure 1.

(a) a treatment wand with passive reflective spherical balls and (b) IR camera to monitor movement of a point in a 3D volume ($205 \times 186 \times 147 \text{ cm}^3$) in OR.

Figure 2.

Fluence rate per power (ϕ/S) inside a spherical water cavity of radius $R_{\text{sph}} = 4$ cm inside tissue with $\mu_a = 0.1 \text{ cm}^{-1}$, $\mu_s = 200 \text{ cm}^{-1}$, and $g = 0.9$ for the source positioned in the center (left plot) and off-center at $0.5R_{\text{sph}}$ (right plot). The attenuation coefficient in the water cavity is 0.0038 cm^{-1} .

Figure 3.

Fluence rate per power (ϕ/S) inside a spherical water cavity of radius $R_{sph} = 4$ cm inside tissue with $\mu_a = 0.1 \text{ cm}^{-1}$, $\mu_s = 200 \text{ cm}^{-1}$, and $g = 0.9$ for the source positioned in the center (left plot) and off-center at $0.5R_{sph}$ (right plot). The attenuation coefficient in the water cavity is 0.05 cm^{-1} .

Figure 4.

Summary of scattered fluence rate per power ($F = \phi/S$) inside a spherical water cavity: (a) F vs. μ_s for water cavity of radius $R_{\text{sph}} = 4$ cm and μ_a , no attenuation inside; (b) F vs. μ_a for water cavity of radius $R_{\text{sph}} = 4$ cm and μ_s , no attenuation inside; (c) F vs. R_{sph} for water cavity without attenuation inside tissue with $\mu_a = 0.1$ cm^{-1} , $\mu_s = 200$ cm^{-1} , and $g = 0.9$; (d) F vs. source off-axis positions for $R_{\text{sph}} = 4$ cm, with and without attenuation (0.0036 cm^{-1} and 0.05 cm^{-1}) inside the water sphere for tissue with $\mu_a = 0.1$ cm^{-1} , $\mu_s = 200$ cm^{-1} , and $g = 0.9$.

Figure 5.

Calculated light fluence at various times using only the direct light (Eq. 1) at 1 s and 3656s after treatment in a Phase II randomized Photofrin-mediated PDT. The final light fluence rate should be 30 J/cm^2 .