Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2013 February 2; 8568: . doi:10.1117/12.2005198.

PDT dose dosimetry for pleural photodynamic therapy

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Abstract

PDT dose is the product of the photosensitizer concentration and the light fluence in target tissue. Although existing systems are capable of measuring the light fluence *in vivo*, the concurrent measurement of photosensitizer in the treated tissue so far has been lacking. We have developed and tested a new method to simultaneously acquire light dosimetry and photosensitizer fluorescence data via the same isotropic detector, employing treatment light as the excitation source. A dichroic beamsplitter is used to split light from the isotropic detector into two fibers, one for light dosimetry, the other, after the 665 nm treatment light is removed by a band-stop filter, to a spectrometer for fluorescence detection. The light fluence varies significantly during treatment because of the source movement. The fluorescence signal is normalized by the light fluence measured at treatment wavelength. We have shown that the absolute photosensitizer concentration can be obtained by an optical properties correction factor and linear spectral fitting. Tissue optical properties are determined using an absorption spectroscopy probe immediately before PDT at the same sites. This novel method allows accurate real-time determination of delivered PDT dose using existing isotropic detectors, and may lead to a considerable improvement of PDT treatment quality compared to the currently employed systems. Preliminary data in patient studies is presented.

Keywords

photodynamic therapy; dosimetry; fluorescence; photosensitizer; patient study; PDT

1. INTRODUCTION

PDT treatment outcome depends on both the light dose and photosensitizer distribution¹. PDT dose is defined as a product of the photosensitizer concentration and the light fluence in target tissue. Although the existing systems are capable of measuring the light fluence *in vivo*, the concurrent measurement of photosensitizer in the treated tissue so far has been lacking.

This study demonstrates the results of ongoing patient study, where the PDT dose was measured using treatment light as a source. The same fiber detector that is employed for light dosimetry was also monitoring HPPH fluorescence *in vivo*, and photosensitizer

concentration was determined by applying optical properties correction to the fluorescence measurements.

2. METHODS

2.1 Patient treatment

The patients in this study were enrolled in a clinical trial of HPPH-mediated PDT for the lung cancer treatment. They were administered 4 mg of HPPH per kg of body weight 48 hours before surgery, and treated with light therapy at 665 nm with a fluence of 25–30 J/cm². Light was delivered via a fiber optic embedded in a modified endotracheal tube filled with dilute intralipid. A dilute intralipid solution, used as a scattering medium, was placed inside the patients' pleural cavity. The fluence rate and cumulative fluence were continuously monitored at seven sites during the treatment using isotropic detectors sewn to the pleural cavity wall², while the eighth isotropic detector was used to measure the light dose and HPPH fluorescence simultaneously. The treatment continued until the prescribed dose was reached at the monitored sites.

2.2 HPPH fluorescence detection during treatment

Treatment light from a diode 665 nm laser (B&W Tek, Newark, DE), source was sensed by an isotropic detector located inside the patient's pleural cavity. A dichroic beamsplitter divided the light between two fibers, one used for light dosimetry, the other for fluorescence measurement. A band-stop filter centered at 658 nm (658 StopLine, Semrock, Rochester, NY) was used to remove most of the treatment light before fluorescence was recorded by a single-channel spectrometer (BTC-112E, B&W Tek, Newark, DE), (Fig. 1).

2.3 Optical properties (OP) correction

The amount of HPPH fluorescence registered by a detector depends on the optical properties of the surrounding tissues. To determine the correction factor for HPPH concentration, absorption and scattering coefficients were measured for several intralipid, ink, and HPPH phantoms³. We have used the empirical OP correction function in the form⁴⁻⁵:

$$CF = (C_{01} + C_{02} \mu_{s'}) / \mu_{s'} * \exp [(b_1 + b_2 \mu_{s'}) \mu_{eff}] \quad (1)$$

where $\mu_{eff} = (3 \mu_a \mu_{s'})^{1/2}$, for semi-infinite geometry with detector located in water on top of a semi-infinite tissue or phantom medium.

Phantom optical properties are summarized in Table 1. Table 2 shows OP correction function parameters extracted from the phantom data fits. Fig. 2a demonstrates the results of applying correction function to the phantoms with constant HPPH concentration, while Fig. 2b shows the linear relationship between HPPH concentration and fluorescence in the variable HPPH phantom after the OP correction.

The OP correction factor was applied to the patient fluorescence data, based on pre-PDT OP measurements. To make sure that fluorescence signal was fully separated from the excitation light, a singular-value decomposition (SVD) was applied to the raw fluorescence data after background subtraction and normalization to the excitation signal.

3. RESULTS AND DISCUSSION

3.1 Patient data and raw fluorescence signal during treatment

So far, we have collected and analyzed data for four patients. Table 3 is the summary of patient data. It should be noted that the initial fluorescence value varies between patients, in part due to the difference between detector locations. The total treatment time depends on the size of the patient's pleural cavity. The optical properties were measured before the PDT treatment.

Fig. 3 shows typical raw fluorescence collected during treatment. The signal intensity at the detector position varied randomly throughout the entire treatment time, depending on the source location. This variation was the reason for further processing of the data before photosensitizer concentration could be obtained.

3.2 Singular-value decomposition: basis vectors and components

Raw fluorescence data was background-subtracted and normalized to the signal around 640 nm, representing excitation light outside of the band-stop filter range. We have also applied thresholding to the data to skip time intervals with near-zero light conditions. Because there was a significant overlap between treatment light and HPPH fluorescence, a secondary fluorescence peak around 720 nm was chosen for data processing, and SVD was used to make sure that fluorescence signal is not contaminated by residual excitation light. Fig. 4 shows SVD basis vectors and decomposition results. HPPH fluorescence components for all four patients are shown in Fig. 5, both in terms of treatment time and cumulative fluence. Based on the smoothed results, we conclude that fluorescence did not change significantly during any of the four cases, decreasing at most by 15% by the end of treatment.

3.3 HPPH concentration during treatment

To obtain HPPH concentration during treatment, the OP correction function for HPPH, used with the patient optical properties data, was applied to the patient HPPH fluorescence SVD⁶. Fig. 6 shows HPPH concentration for patients #3 and #4. In both cases, photosensitizer concentration tends to decrease slightly (10 – 15%) over the course of the treatment. The absolute HPPH concentration, however, is different by a factor of seven between these patients.

4. CONCLUSIONS

We have demonstrated that photosensitizer fluorescence can be measured in clinical situations using existing isotropic detectors for light dosimetry. Fluorescence signal varied considerably during treatment, requiring extensive data processing. The HPPH concentration could be determined from fluorescence data using optical properties correction function.

In our clinical study, the amount of HPPH in the tissues did not change significantly during treatment time. However, we have observed HPPH concentration variation of a factor of seven among different patients.

Future plans include fluorescence collection at several detector locations per patient, real time processing of fluorescence data, and optimization of the OP correction function.

Acknowledgments

The authors would like to thank the physicians Keith Cengel, Chuck Simone, and Joseph Friedberg for clinical insight; the PDT team at Penn and Presbyterian Hospital for their help with PDT treatment; particularly, Andreea Dimofte for calibration and dosimetry measurements, Carmen Rodriguez and Michele Kim for detector sterilization, Julien Menko for equipment transportation, and Melissa Culligan for equipment logistics. This work is supported by the national Institute of Health (NIH) grants P01 CA87971 and R01 CA154562.

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Figure 1. Schematic diagram (a) and photograph (b) of the simultaneous light dose and photosensitizer fluorescence measurement setup.

Figure 2.

(a) HPPH 0.5 mg/kg phantom: SVD with (dashed) and without (solid) optical properties correction; (b) HPPH fluorescence SVD signal as a function of HPPH concentration for a phantom with variable HPPH.

Figure 3.

(a) Typical raw HPPH fluorescence spectra collected during PDT treatment; (b) Fluorescence peak at 720 nm as a function of cumulative fluence.

Figure 4.

(a) SVD basis vectors with band-stop filter: treatment laser light (blue) and HPPH fluorescence (green); (b) Results of SVD for typical patient data: treatment laser component (solid blue), HPPH fluorescence (solid green), background/Fourier component (solid red), and smoothed HPPH (dashed).

Figure 5.

Patient HPPH SVD components (plus smoothing) as a function of treatment time (a) and cumulative fluence (b); patients #1 (X), #2 (+), #3 (*), and #4 (Δ).

Figure 6.
Patient HPPH concentration as a function of treatment time (a) and cumulative fluence (b) for patients #3 and #4.

Table 1

Phantom optical properties summary for the treatment wavelength ($\lambda = 665$ nm).

Optical properties	Intralipid	Ink	HPPH
Absorption coefficient μ_a , 1/cm	0.007 $\pm$ 0.021	36.28*C(%)	0.061*C(mg/kg)
Scattering coefficient μ_s' , 1/cm	11.26*C(%)	0	0

Table 2

Optical properties correction function parameters.

C_{01}	C_{02}	b_1	b_2
-0.7645	0.1919	0.5662	-0.0213

Table 3

A summary of patient data.

Patient Index	Treatment time, min	Total fluence, J/cm ²	Initial raw fluorescence, arb. units	Absorption coeff, 1/cm	Scattering coeff, 1/cm
1	48	25	4.0	N/A	N/A
2	45	25	2.2	N/A	N/A
3	54	30	6.5	0.025	1.61
4	46	30	2.5	0.31	11.5