Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2016 March 17; 9694: 96940Y-. doi:10.1117/12.2213401.

PDT Dose Dosimeter for Pleural Photodynamic Therapy

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Abstract

PDT dose is the product of the photosensitizer concentration and the light fluence in the target tissue. For improved dosimetry during plural photodynamic therapy (PDT), a PDT dose dosimeter was developed to measure both the light fluence and the photosensitizer concentration simultaneously in the same treatment location. Light fluence and spectral data were rigorously compared to other methods of measurement (e.g. photodiode, multi-fiber spectroscopy contact probe) to assess the accuracy of the measurements as well as their uncertainty. Photosensitizer concentration was obtained by measuring the fluorescence of the sensitizer excited by the treatment light. Fluence rate based on the intensity of the laser spectrum was compared to the data obtained by direct measurement of fluence rate by a fiber-coupled photodiode. Phantom studies were done to obtain an optical property correction for the fluorescence signal. Measurements were performed in patients treated Photofrin for different locations in the pleural cavity. Multiple sites were measured to investigate the heterogeneity of the cavity and to provide cross-validation via relative dosimetry. This novel method will allow for accurate real-time determination of delivered PDT dose and improved PDT dosimetry.

Keywords

photodynamic therapy; PDT dose; pleural PDT; Photofrin

1. INTRODUCTION

Improving dosimetry for photodynamic therapy (PDT) is an ongoing goal for use in the treatment of cancer and other localized diseases. Type II PDT is a multi-faceted, dynamic process that involves the interactions of light, photosensitizer, and ground state oxygen ($^3\text{O}_2$), to create reactive singlet oxygen ($^1\text{O}_2$) [1]. PDT dose has been used as a dosimetric quantity in clinical settings for some time. PDT treatment outcome depends on both the light dose and the photosensitizer concentration, and PDT dose is a quantity that incorporates both as a product. Light dose alone is not a sufficient dosimetric quantity in clinical settings while it can be used *in vitro* [2–4]. Heterogeneities in both light and photosensitizer concentration add to challenges in dosimetry [5]. Existing real-time dosimetry has been with focused on light fluence *in vivo*, but with concurrent measurement of the photosensitizer in treated tissue, PDT dose can be evaluated in real time.

2. MATERIALS AND METHODS

2.1 Clinical Trial

In a phase II/III randomized clinical trial, patients with pleural mesothelioma received lung-sparing surgery in conjunction with PDT on one arm, while patients on other randomized arm received only the surgery. For those patients receiving PDT, Photofrin (Pinnacle Biologics, Chicago, IL, USA) was administered at a dose of 5 mg per kg of body weight 24 hours before surgery. PDT treatment was performed with 632 nm light to a total fluence of 60 J/cm². Light was delivered via a bare optical fiber embedded in a modified endotracheal tube filled with 0.1% Intralipid. The pleural cavity was also filled with Intralipid to aid with light scattering.

2.2 PDT Dose Dosimeter Instrumentation

Isotropic detectors (Medlight, Switzerland) were used to collect light fluence data during treatment. Eight locations within the pleural cavity were chosen to represent the entire area, and isotropic detectors were sutured onto the pleural cavity surface. Light fluence rate and cumulative fluence were monitored during PDT to determine the delivered dose.

Two of the eight isotropic detectors were used in the PDT dose dosimeter system. Bifurcated optical fibers (Ocean Optics, Inc., Dunedin, FL, USA) were coupled to the isotropic detectors. One arm of the bifurcation was connected to the dosimetry system to do the light dosimetry measurements. The other arm of the bifurcation was connected to a 633 nm RazorEdge long-pass filter (Semrock, Inc., Rochester, NY, USA) to block the treatment light and then the CCD spectrometer (Exemplar, B&W Tek, Inc., Newark, DE, USA). A schematic of the set-up is shown in figure 1.

2.3 Spectroscopy

Fluorescence spectra were collected with a single channel CCD spectrometer. To investigate the fluorescence excited by the treatment light (632 nm), a long-pass filter was used to only allow signal after 633 nm. The raw spectrum was fitted to the basis spectrum of Photofrin and the laser spectrum using single value decomposition (SVD) fitting and comparing spectra to those from phantoms with known concentrations of photofrin. An optical property correction factor was applied to each phantom

2.4 Optical Property Correction

Fluorescence signal registered by the spectrometer is affected by the optical properties of the surrounding tissues. To determine the correction factor for Photofrin concentration as measured by fluorescence, absorption and scattering coefficients (μ_a and μ_s' respectively) were measured for several Intralipid, ink, and Photofrin phantoms [6, 7]. An empirical optical property correction function of the following form was used:

$$CF = \frac{C_{01} + C_{02}\mu_s'}{\mu_s'} \cdot \exp \left[(b_1 + b_2\mu_s')\mu_{eff} \right]$$

where $\mu_{eff} = (3\mu_a\mu_s')^{1/2}$ for a semi-infinite geometry with a detector located in water on top of a semi-infinite tissue or phantom medium. To test the accuracy of this model, a set of experiments in tissue-simulating phantoms were designed. These phantoms contained Intralipid (Fresenius Kabi, Germany) as a scatterer and Parker Quink (Parker Pen Company, UK). In three separate phantoms with different Intralipid concentrations, varying amounts of ink were added to change the μ_a . The Photofrin concentration was held constant at 3 mg/kg. A summary of the phantom properties are in table 1.

A fourth phantom was used with increasing amounts of Photofrin to test the correction factor as well as to obtain a calibration curve between the fitted SVD and the concentration of photosensitizer added.

3. RESULTS

Sensitizer concentration for two different sites in the pleural cavity were determined for the treatment time for two patients. The parameters for the optical property correction factor were determined using the function *fminsearch* in Matlab (Mathworks, Natick, MA, USA). The parameters are summarized in table 2, and the correction results are shown in figure 2.

Spectra can be separated into their SVD fitted components, laser spectra and Photofrin fluorescence spectra, as shown in figure 3.

A selection of raw spectra from a patient can be seen in figure 4. As seen here, the signal is very noisy with a great deal of spectra with no significant Photofrin signal. Spectra are being collected continuously throughout the treatment time, even when there is no light on the site of interest.

Photofrin concentration in patients were calculated for each patient data set. Gaps in data represent when the laser was off for a break in treatment or spectra was not collected. Preliminary results can be seen in figure 5.

Fitting of the laser component and comparison with fluence rate data showed when the laser was near the detector of interest. Threshold levels of laser light spectra can be used to filter data along with light fluence data collected by the light dosimetry system.

Future systems will involve a more efficient data collection system so that spectra collected when there is no treatment light at the site of the detector, the data is not saved. Currently the most time consuming portion of the data analysis is in data organization and selection. Real-time display of sensitizer concentration is a goal of this project so that the physician can not only see the light being delivered to a location inside the pleural cavity but also the amount of photosensitizer that is present. More channels are being developed so that sensitizer can be investigated for multiple sites.

4. CONCLUSION

A PDT dose dosimeter was developed and used during pleural PDT using Photofrin. It has been 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 Photofrin concentration could be determined from fluorescence data using optical properties correction function. In this preliminary study, the amount of Photofrin in tissue did not change significantly during the treatment time. However, future plans include collection of fluorescence data at several detector locations per patient, as well as real time processing and optimization.

Acknowledgments

The authors would like to thank Keith Cengel, Charles B. Simone II, Sunil Singhal, Andreea Dimofte, and Carmen Rodriguez for their help with the clinical aspect of the study. This work is supported by grants from the National Institute of Health (NIH) R01 CA154562 and P01 CA87971.

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Figure 1. Schematic of the PDT dose dosimeter system set up. The photograph shows the components used.

Figure 2.

(a) Photofrin 3 mg/kg phantom SVD with and without the optical property correction (b) Photofrin fluorescence SVD signal as a function of Photofrin concentration for a phantom with varying amounts of Photofrin

Figure 3.
Fluorescence spectra separated into their spectral components

Figure 4.
Typical raw fluorescence spectra of Photofrin collected during PDT treatment.

Figure 5.
Photofrin concentration of two patient cases plotted over time.

Table 1

Phantom conditions

Phantom	1	2	3	4
Intralipid (%)	0.5	1.0	1.5	1
Photofrin (mg/kg)	3	3	3	0 – 10
Ink (%)	0 – 1	0 – 1	0 – 1	0.6

Table 2

Optical property correction function parameters

Constant	C_{01}	C_{02}	b_1	b_2
Value	1.4545	0.7245	1.902	-0.1477