Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2006 January 21; 6139: . doi:10.1117/12.646220.

***In-vivo* light dosimetry of interstitial PDT of human prostate**

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Abstract

We report results of in-vivo light dosimetry of light fluence (rate) in human prostate during photodynamic therapy (PDT). Measurements were made in-vivo at the treatment wavelength (732nm) in 15 patients in three to four quadrants using isotropic detectors placed inside catheters inserted into the prostate. The catheter positions are determined using a transrectal ultrasound (TRUS) unit attached to a rigid template with 0.5-cm resolution. Cylindrical diffusing fibers with various lengths are introduced into the catheters to cover the entire prostate gland. For the last four patients, distributions of light fluence rate along catheters were also measured using a computer controlled step motor system to move multiple detectors to different distances (with 0.1 mm resolution). To predict the light fluence rate distribution, a kernel-based model was used to calculate light fluence rate using either (a) the mean optical properties (assuming homogeneous optical properties) for all patients or (b) using distributions of optical properties measured for latter patients. Standard deviations observed between the calculations and measurements were 56% and 34% for (a) and (b), respectively. The study shows that due to heterogeneity of optical properties significant variations of light fluence rate were observed both intra and inter prostates. However, if one assume a mean optical properties ($\mu_a = 0.3 \text{ cm}^{-1}$, $\mu_s' = 14 \text{ cm}^{-1}$), one can predict the light fluence rate to within a maximum error 200% for 80% of the cases and a mean error of 105%. To improve the prediction of light fluence rate further would require determination of distribution of optical properties.

Keywords

In-vivo light dosimetry; fluence rate; prostate PDT

I. INTRODUCTION

Photodynamic therapy (PDT) is a treatment modality employing light of an appropriate wavelength in the presence of oxygen to activate a photosensitizing drug which then causes localized cell death or tissue necrosis. Using a surface illumination technique, PDT has been used to treat many superficial tumors including skin, lung, esophagus, and bladder (1). This technique is, however, inadequate when applied to large bulky tumors or solid organs due to limited light penetration into tissue. A more efficient illumination scheme would be

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interstitial light delivery whereby optical fibers are placed directly into the bulky tumors or organs.

The prostate gland is an organ that appears to be a good target for interstitial PDT. Tumors of the prostate are often confined to the prostate itself and brachytherapy techniques used for the placement of radioactive seed implants can be adapted for the placement of interstitial optical fibers (2). Several preclinical studies have evaluated the feasibility of delivering PDT to the prostate via this interstitial approach (3–7). The development of this light delivery technique has necessitated an improved understanding of light dosimetry, critical in planning the configuration of multiple fibers within the organ or tumor. Based on results of a preclinical study in canine (8), we have initiated a motexafin lutetium (MLu)-mediated PDT of the prostate in human at University of Pennsylvania.(9) MLu is a second generation synthetic photoactive drug that has a Q-band absorption peak at 732 nm. (10–11) Ideal optimization of the photodynamic linear light sources depends on knowledge of the spatial distributions of (1) tissue light opacity within the prostate, (2) photosensitizing drug, and (3) oxygen within tissue. Since these spatial distributions can vary in time, measurements must be done to monitor the process, and feedback mechanisms must be developed to optimize PDT dose. The most effective method of the feedback mechanism is to adjust the light source strengths to compensate for the light fluence rate variation over time. To do so, an effective method to determine the light fluence rate in threedimensions *in-vivo* is important.

Our study focused on the prediction of light fluence rate distribution in the human prostate during PDT. A model was developed to calculate the light fluence rate in 3D volume. The calculations and measurements were examined in 15 patients. A study of the inhomogeneous light-opacity distribution *in vivo* is performed and reported elsewhere. (12–13)

II. METHODS AND MATERIALS

1. In-vivo light fluence rate measurements in human prostate

A Phase I clinical trial of motexafin lutetium (MLu)-mediated PDT in patients with locally recurrent prostate carcinoma was initiated at the University of Pennsylvania. The protocol was approved by the Institutional Review board of the University of Pennsylvania, the Clinical Trials and Scientific Monitoring Committee (CTSRMC) of the University of Pennsylvania Cancer Center, and the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. A total of 16 patients were treated, of which 15 patients have undergone in-vivo light fluence rate measurements. Each patient who signed the informed consent document underwent an evaluation, which included an MRI of the prostate, bone scan, laboratory studies including PSA (prostatic specific antigen), and a urological evaluation. Approximately two weeks prior to the scheduled treatment a transrectal ultrasound (TRUS) was performed for treatment planning. An urologist drew the target volume (the prostate) on each slice of the ultrasound images. These images were spaced 0.5 cm apart and were scanned with the same ultrasound unit used for treatment.

A built-in template with a 0.5-cm grid projected the locations of possible light sources relative to the prostate. A treatment plan was then prepared to determine the location and length of light sources. Cylindrical diffusing fibers (CDF) with active lengths 1-5 cm were

used as light sources. The sources were spaced one centimeter apart and the light power per unit length was less than or equal to 150 mW/cm^2 for all optical fibers. The length of the CDF at a particular position within the prostate was selected to cover the full length of the prostate (see Fig. 1a). The final plan often required that the prostate be divided into four quadrants. Four isotropic detectors were used, each placed in the center of one quadrant. A fifth isotropic detector was placed in a urethral catheter to monitor the light fluence in the urethra (Fig. 1b).

The patients were anesthetized in the operating room with general anesthesia to minimize patient movement during the procedure. Transrectal ultrasound-guided biopsies for MLu measurements were obtained prior to light delivery. The ultrasound unit was used to guide needle placement in the operating room. A template was attached to the ultrasound unit and was matched to the same 5-mm grid used for treatment planning (Fig. 1b).

Four detector catheters (one for each quadrant) were inserted into the prostate. These detectors were kept in place during the entire procedure of PDT treatment. Four additional pre-planned treatment catheters for cylindrical diffusing fiber light sources were then inserted 0.5 or 0.7 cm away from the detector catheters (Fig. 1b). The source catheters were used for light delivery and point source measurements. A 15-W diode laser, model 730 (Diomed, Ltd., Cambridge, United Kingdom) was used as the 732 nm light source. The detector position in each quadrant was varied to obtain the peak light fluence rate within the quadrant.

Isotropic detectors with scattering tips were used for all measurements (14). Each isotropic detector was calibrated in air in an integrating sphere right before the light fluence rate measurement with an accuracy of $\pm 5\%$. A tissue correction factor of 2.0 was applied to all data to correct for detector signal reduction due to changes in index of refraction (15).

To evaluate the distribution of light fluence rate, a point source was introduced in the prostate before and after PDT for selected patients. The distance dependence of light fluence rate was measured using a motorized isotropic detector (13). The distance dependence was modeled using a point source model in a homogeneous and infinite medium to determine the optical properties at the location of measurement. A summary of measurements made are listed in Table 1.

2. Kernel-based 3D light fluence rate calculation in homogeneous medium

The transport scattering (μ'_s) and absorption (μ_a) coefficients characterize the scattering and absorption properties of tissue. With the diffusion approximation, the light fluence rate ϕ at a distance r from a point source of power, S , can be expressed as (16)

$$\phi = \frac{S \cdot \mu_{eff}^2}{4\pi r \cdot \mu_a} \cdot e^{-\mu_{eff} \cdot r} = \frac{S \cdot 3\mu_s'}{4\pi r} \cdot e^{-\mu_{eff} \cdot r} \quad (1)$$

where S is the power of the point source (in mW); $\phi(r)$ is the fluence rate in mW/cm^2 ;

$\mu_{eff} = \sqrt{3 \cdot \mu_a \cdot \mu_s'}$ (27) is the effective attenuation coefficient in tissues and is applicable for a wider range of μ_a and μ_s' combinations than the traditional definition of

$\mu_{eff} = \sqrt{3 \cdot \mu_a \cdot (\mu'_s + \mu_a)}$ (17). The fluence rate for a point source is termed a kernel since any light source geometry can be constructed as a convolution of point sources.

For a cylindrical diffusing fiber (CDF) with length l , the light fluence rate can be calculated by a superposition of Eq. (1):

$$\phi = \sum_{i=1}^N \frac{s \cdot \Delta x \cdot \mu_{eff}^2 \cdot e^{-\mu_{eff} \cdot r_i}}{4\pi \mu_a r_i} = \frac{sl\mu'_s}{4\pi} \cdot \left(\frac{1}{N-1} \sum_{i=1}^N \frac{e^{-\mu_{eff} \cdot r_i}}{r_i} \right) \quad (2)$$

where s is the energy released by light per unit time per unit length, also called unit length source strength (mW/cm). $r_i = \sqrt{x_i^2 + h^2}$, where $x_i = (i-1 - (N-1)/2) \cdot x$ and h is the perpendicular distance from the center of the linear fiber. x is the length step of point sources and N (odd integer) is the number of equal spaced point sources used in the summation (parenthesis in Eq. (2)). The numerical value of the summation should be independent of N (or x) if N is large enough. We found that accurate results of the summation can be obtained if $x = 0.1$ cm or $N = 25$ for $l = 2.5$ cm. In all our calculations $N = 201$ was used. The two free parameters (μ_a and μ'_s) are inherently separable in that for a CDF with a given length: the magnitude of the fluence rate near the light source ($h = 0$) is determined by μ'_s only and the slope of the spatial decay of the light fluence rate is determined by μ_{eff} only.

In theory, measurements of ϕ at two different distances r from the point source with known unit length source strength s and length l are sufficient to determine both μ_a and μ'_s . Measurements at multiple sites allow evaluating the variation of these optical characteristics within the prostate volume. Since Eq. (1) is a non-linear equation of two free parameters μ_a and μ'_s , we used a differential evolution algorithm developed by Storn *et al* (18). We modified the algorithm to require that all parameters (μ_a and μ'_s) are positive (19). The optical properties measured in 13 patients have been published elsewhere (12). Overall μ_a varied between $0.07 - 1.62 \text{ cm}^{-1}$ (mean $0.3 \pm 0.2 \text{ cm}^{-1}$) and μ'_s varied between $1.1 - 44 \text{ cm}^{-1}$ (mean $14 \pm 11 \text{ cm}^{-1}$). The effective attenuation coefficient μ_{eff} varied between $0.91 - 6.7 \text{ cm}^{-1}$, corresponding to an optical penetration depth ($\delta = 1/\mu_{eff}$) of $0.2 - 1.1$ cm. The mean values of μ_{eff} and δ were $2.9 \pm 0.8 \text{ cm}^{-1}$ and 0.4 ± 0.1 cm, respectively.

The distance dependence of light fluence rate per source power, ϕ/S , for all point source measurements was evaluated to determine its variation. ϕ/S is also compared with the dose rate distribution from an I-125 isotope source using AAPM TG43 formalism (20).

III. RESULTS AND DISCUSSIONS

Typical results of light fluence rate measured during PDT were shown in Fig. 2. The light fluence rate usually does not change with time. In Fig. 2, one detector position was moved during measurement, resulting in a disturbance of light fluence rate. It is clear that the mean light fluence rate varies from locations to locations in the same patient, reflecting heterogeneity of optical properties in prostate. A summary of the peak fluence rate among patients in the four quadrants are listed in Table 1. Notice that the data in Table 1 has been

corrected by the detector tissue correction factor of 2.0 to account for change of detector sensitivity in different medium (15).

The peak fluence rate varies by 24 times from a minimum of 26 to a maximum of 634 mW/cm² (see Table 1). The variation within a prostate at different locations was as large as the variation among prostates. We attribute these variations to heterogeneity of optical properties.

Large variations of depth dependence of light fluence rate per source power (ϕ/S) were observed for point source measurements (Fig. 3). The mean curve corresponds to an optical properties of $\mu_a = 0.3 \text{ cm}^{-1}$, $\mu_s' = 14 \text{ cm}^{-1}$. Clearly there is a wide variation of the depth dependence of ϕ/S due to heterogeneities of optical properties.

The light fluence rate dependence for the mean optical properties is very similar to the dose rate depth dependence of I-125 isotope within 1 cm from the point source (Fig. 4a). For longer distance scales, the light fluence rate drops much faster than the radiation isotope source (Fig. 4b). Since the effective treatment range is between 0 and 1 cm, one can justify the use of a Brachytherapy treatment planning system designed for the permanent prostate implant to perform preplan for photodynamic therapy in prostate.

Figure 5 compares the light fluence rate at 0.5 cm, a typical prescription point, from a point source. The mean and standard deviation of light fluence rate at 0.5 cm from a point source is $1.48 \pm 1.13 \text{ cm}^{-2}$. This variation is not as large as the variation of optical properties, μ_a varied between 0.07 and 1.62 cm⁻¹ and μ_s' varied between 1.1 and 44 cm⁻¹. There are instances, e.g., #6, when the variation of light fluence rate within a patient is larger than the mean variation among patients.

Using the measured mean optical properties and the kernel-based fluence rate calculation, one can determine the 3D light fluence rate distribution for a specific source loading (Fig. 6). Figure 6a shows the iso-fluence lines for the distribution for 100 J/cm² for a treatment time of 1353 second using CDF of the same source strength of 150 mW/cm. The peak light fluence rates at the detector locations as well as the urethra (x) were also calculated to be compared with the actual measurement. Figure 6b shows the calculated light fluence profile along the catheter (z direction) of the prostate. It is not surprising that the light fluence rate in urethra (256.6 mW/cm²) is in the same order as the peak fluence rate at the prescription points (221.7 – 327.8 mW/cm²). We have never measured light fluence rate from urethra, probably because of the detector placement error.

We compared the calculations with measurements for light fluence rate profile at the detector location in the right upper quadrant (RUQ) and right lower quadrant (RLQ) in one patient, shown in Fig. 7. The agreement between measurement (solid line) and the calculation (dashed line) for this particular patient is quite good. There are some features for the RLQ that was not present in the calculation. This latter difference is not surprising since one expects to see heterogeneity of optical properties, which will then affect the light fluence rate distribution.

To quantify the agreement among patients, we compared the measured light fluence rate and calculation for all patients treated using either the mean optical properties or the actual mean optical properties measured for the specific quadrant before the PDT treatment (Fig. 8). The histogram of error is shown in Fig. 9a and 9b for the mean optical properties () and the actual mean optical properties, respectively. The mean error is 105.6% using the mean optical properties and 85% using the patient specific optical properties. Most of the error falls within 200% for either the mean or the actual optical properties. The few outlying errors (e.g., 600% for patient #3 in Fig. 8b) are believed to be due to bleeding in the prostate, which is excluded for optical properties determination. It is not surprising that we can only achieve a mean error of 85% because of the heterogeneity of optical properties in patients. To further improve the agreement between calculation and measurement, it is necessary to account the distribution of optical properties within each patient.

The comparison between calculation and measurement using the measured optical properties were performed for one patient using finite-element method. Details of the calculation are described elsewhere (21). With the optical properties accounted for, the maximum error is now reduced to 20%. Further studies are necessary to accumulate more data to improve the fluence rate calculation in heterogeneous media as well as to quantify the agreement in three-dimensions. In addition, a fast kernel-based calculation algorithm is to be developed to speed up the calculation. Currently the finite-element calculation requires a typical 300 seconds to complete a calculation.

IV. CONCLUSION

We have measured light fluence rate *in-vivo* at various points in human prostates during PDT. The peak light fluence rate at the prescription point varied by 24 times (26 – 634 mW/cm²) for the same source loading at 732 nm, thus a real-time dosimetry system is necessary to quantify the light fluence rate *in vivo*. We found that for the mean optical properties, the light fluence rate distribution is similar to the dose rate distribution for I-125, making it possible to make preplans using I-125 to ensure volumetric coverage of light to the prostate. We compared measurement with calculation and found that light fluence rate calculation based on the mean homogeneous optical properties can predict the light fluence rate to a mean error of 86%. When calculation is performed based on heterogeneous optical properties, this agreement improved to 20%.

ACKNOWLEDGMENT

This work is supported by grants from Department of Defense (DOD) DAMD17-03-1-0132 and National institute of health (NIH) P01 CA87971 and R01 CA109456.

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Figure 1.

(a) Schematic of placement of light source and detectors for prostate PDT. The prostate template was drilled with a 5-mm equal spaced grid. Cylindrical diffusing fibers (CDF) were inserted into the catheters to illuminate the entire prostate gland. Four isotropic detectors (not shown) are placed in one of the catheters to detect the light fluence rate. (b) Schematics of the relative positions between a CDF and four isotropic detectors overlaid on the US image on the 0.5-cm Template for patient #13. The detector positions are labeled as RUQ, LUQ, RLQ, and LLQ for right upper quadrant, left upper quadrant, right lower quadrant, left lower quadrant, respectively.

Figure 2.

Light fluence rate vs. time measured in-vivo for patient #7. Note that the tissue detector correction factors were not applied in this plot, i.e., the true light fluence rate should be increased by 2.0 times.

Figure 3.

The depth dependence of ϕ/S for all point measurements (dotted lines). The solid line is the depth dependence for the mean optical properties ($\mu_a = 0.3 \text{ cm}^{-1}$, $\mu_s' = 14 \text{ cm}^{-1}$). The dashed lines are for the most penetrative optical properties (top, $\mu_a = 0.04 \text{ cm}^{-1}$, $\mu_s' = 30 \text{ cm}^{-1}$) and the least penetrative optical properties (bottom, $\mu_a = 1.5 \text{ cm}^{-1}$, $\mu_s' = 9 \text{ cm}^{-1}$).

Figure 4.

Comparison of depth dependence of light fluence rate (solid line) for the mean optical properties ($\mu_a = 0.3 \text{ cm}^{-1}$, $\mu_s' = 14 \text{ cm}^{-1}$) and the dose rate distribution for I-125 (dashed line). (a) Linear plot between 0 – 1 cm from the point source. (b) Log plot between 0 – 5 cm from the source.

Figure 5.

Comparison of light fluence rate per source power at 0.5 cm from the point sources measured in different patients. The bar indicate the mean value of light fluence rate before (first bar) and after (second bar) PDT. The error bar is $\pm$ s.d. (standard deviation) of the mean value. The dark solid line and the dark dashed lines indicate the mean and standard deviation of ϕ/S in all patients: $1.48 \pm 1.13 \text{ cm}^{-2}$.

Figure 6.

Calculated light fluence rate distribution superimposed on an ultrasound image of prostate cross-section at depth of 0.5 cm, which was used in PDT planning. The outer white line indicates the predicted 100% isodose line and the inner blue line is the contour of the prostate. The "o" symbols represent the source positions and the predicted light fluence rates at "x" symbol positions are displayed next to the symbols. (b) Light fluence rates along the z direction at the detector positions and in the urethra.

Figure 7. Comparison of light fluence rates along z direction in a patient prostate between measurements and predictions using the mean optical properties in patient #17: (a) RUQ and (b) RLQ.

Figure 8.

Light fluence rates calculated using actual source strengths, with measured optical properties and the mean optical properties, respectively. (a) RUQ, (b) LUQ, (c) RLQ, and (d) LLQ.

Figure 9.

Histograms of the errors in 14 patients for calculations using: (a) assumed source strength of 150 mW/cm and the mean optical properties; (b) actual source strengths and measured optical properties.

Figure 10. Comparison of light fluence between calculation and measurement for a patient accounting for the optical properties distribution. (a) Comparison of the light fluence rate profile and (b) distribution of error between the two.

Table 1

Number of patients with point source measurements performed at 732 nm *in-vivo* in prostate.

	RUQ	LUQ	RLQ	LLQ
Before PDT	9	6	6	5
After PDT	6	4	6	5
After/Before PDT	5	4	5	4
Total	15	10	12	10

Table 2

Summary of the peak in-vivo light fluence rate measured at 732 nm in human prostate.

Patient #	Maximum ϕ (mW/cm ²)			
	RUQ	LUQ	RLQ	LLQ
2	238	220	395.6	322.6
3	317.8	26	—	—
4	260	50	116	56
5	300	674	350	474
6	286.6	286.6	270	286.6
7	320	80	72	92
8	57.4	13.6	84	20.2
9	70	392.6	46	104
10	438	438	240	160
11	36.2	59.6	111.2	170
12	120	150	102	176
13	192	28	634	322
15	184	300	202	36