Optical dosimetry in photodynamic therapy of human uterus and brain

Steen J. Madsen [a], Lars O. Svaasand [b], Henry Hirschberg [c], Yona Tadir [d], Bruce J. Tromberg [d]

[a]Dept. of Health Physics, Univ. of Nevada, Las Vegas, 4505 Maryland Pkwy, Box 453037, Las Vegas, NV 89154

[b]Norwegian University of Science and Technology, 7000 Trondheim, Norway

[c]Dept. of Neurosurgery, Rikshospitalet , and Dept. of Oncology, The Norwegian Radium Hospital, Oslo, Norway

[d]Laser Microbeam and Medical Program (LAMMP), Beckman Laser Institute and Medical Clinic, University of California, Irvine, CA 92715

ABSTRACT

Optical "dose" is one of the fundamental parameters required in the design of an efficacious regimen of photodynamic therapy (PDT). The issues involved in delivering a sufficient optical dose to the human uterus and brain during PDT will be discussed. Specifically, measurements of optical properties and fluence rates in excised human uteri are presented. Measured fluence rates are compared to the predictions of a simple diffusion model and the clinical utility of the treatment is discussed. The delivery of light to brain tissue via a surgically implanted balloon applicator will also be considered. The time required to deliver an adequate dose is calculated based on known optical properties and diffusion theory.

Keywords: Photodynamic therapy, optical dosimetry

1. INTRODUCTION

The efficacy of photodynamic therapy (PDT) depends, in part, on the spatial distribution of light within the irradiated tissue. Determination of the spatial distribution of light and, hence, the "optical dose" may be accomplished if the optical properties of the tissue are known. From a clinical point of view, the optical properties (absorption, μ_a, and transport scattering, μ'_s, coefficients) of irradiated tissue should be determined noninvasively. Alternatively, in the absence of a priori knowledge of tissue optical properties, the optical dose may be monitored directly during treatment.

The feasibility of uterine and brain PDT is discussed. In both cases, treatment efficacy depends, in part, on the light distribution in a three-dimensional cavity; spherical in the case of the brain, and cylindrical in the case of the uterus. The goal of intracranial PDT is to deliver an adequate optical dose to the resected tumor margin, while the aim of uterine PDT is to destroy the endometium. Using these tissues as examples, the clinical practicality of optical property measurements, and possible alternatives will be discussed.

Surgical removal of the uterus (hysterectomy) is the most common major operation in the U.S., and dysfunctional uterine bleeding is one of the primary clinical indications for surgical intervention[1]. Endometrial ablation is a possible alternative to hysterectomy for abnormal uterine bleeding produced by benign changes in physiology. However, present ablation techniques have yielded imperfect results[2]. PDT may be a viable alternative for selective destruction of the endometrium without the risks of anaesthesia or the costs of hospitalization.

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The human endometrium is particularly well suited to PDT[3]. First, both drug and light can be easily administered using topical sensitizer and transvaginal optical fiber illumination. Second, the endometrium is relatively thin – 2 to 5 mm depending on the phase of the menstrual cycle[4]. This corresponds favorably to the penetration depth of red light in many tissues. Thus, in principle, a PDT threshold light dose can easily be delivered to the endometrium while sparing the underlying myometrial tissue.

The poor prognosis for patients with malignant brain neoplasm has led to a search for better treatment modalities. Although gliomas are considered to be disseminated tumors, most recur at the site of the previous tumor resection[5]. Improved local control would therefore be of clear benefit. PDT may prove to be useful in the treatment of gliomas as it has the potential to destroy the nests of tumor cells left in the resection border while minimizing damage to normal brain tissue. A treatment regimen comprised of high dose rate brachytherapy and PDT using an indwelling balloon catheter has recently been described[6]. The utility of this applicator in PDT of the brain will be discussed.

2. Theory

2.1. Determination of optical properties

2.1.1. Frequency measurements

In principle, it should be possible to measure the optical properties of uterine tissues non-invasively using frequency domain photon migration (FDPM) techniques[7]. In FDPM, light is launched into multiple scattering media resulting in the propagation of diffuse photon density waves. Density wave phase lag and demodulation amplitude are measured with respect to the source response. These measurable properties are functions of the angular modulation frequency (ω), source-detector separation (r) and tissue optical properties. The optical properties are obtained by fitting appropriate diffusion theory models to the experimental data. The exact form of the diffusion equation will depend on the particular measurement geometry. In an infinite tissue-like medium, at sufficiently low modulation frequency ($\omega << \mu_a$), the phase velocity of the photon density waves (V_p) reaches a dispersionless lower limit independent of modulation frequency[7]:

$$V_p = 2\mu_a c\delta \tag{1}$$

where c is the speed of light in tissue (n = 1.40) and δ is the dc penetration depth,

$$\delta = \left[3\mu_a\left(\mu_a + \mu_s'\right)\right]^{-1/2} \tag{2}$$

The phase velocity and phase slope (slope of phase vs. frequency plot) are related by[7]:

$$\alpha = \frac{r}{V_p} \tag{3}$$

where α is the phase slope. Thus measurement of the phase slope as a function of fiber separation yields V_p.

2.1.2. Steady-state measurements

If the source and detector fibers are separated by a sufficient distance such that diffusion theory is valid, the fluence rate (ϕ) will decay exponentially with source-detector separation:

$$\phi(r) = \frac{\phi_o}{r}\exp\left(-\frac{r}{\delta}\right) \tag{4}$$

where ϕ_o is the fluence rate at some initial separation. Thus a plot of $\ln\left(\frac{\phi_o}{r\phi(r)}\right)$ vs. r yields a straight line with slope $1/\delta$.

2.2. Fluence calculations

The irradiation geometry is shown in Fig. 1. In the cylindrically symmetric case where a long cylindrical applicator is positioned coaxially in a uterine cavity, the fluence rate is given by[2]:

$$\phi = \frac{P\delta c}{2\pi a D K_1(a/\delta)} \cdot K_o(r/\delta) \tag{5}$$

where P is the optical power per unit length of the applicator, a is the radius of the cylindrical cavity, K_o and K_1 are the modified Bessel K functions of the zeroeth and first order, and D is the optical diffusivity:

$$D = \frac{c}{3(\mu_a + \mu_s')} \tag{6}$$

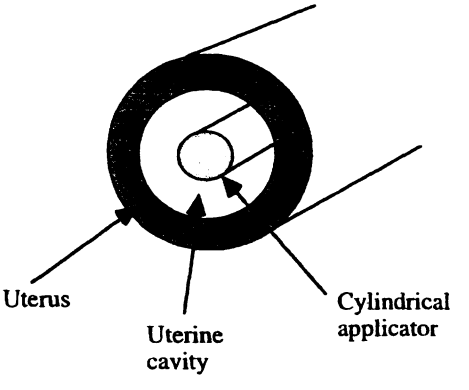

Figure 1. Applicator in a uterine cavity of cylindrical geometry

In the case of an isotropic applicator positioned centrally in a spherical cavity, the fluence rate is given by[2]:

$$\phi = \left[\frac{P_t c}{4\pi a D r(1/a + 1/\delta)}\right] e^{-(r-a)/\delta} \tag{7}$$

where P_t is the total optical power from the applicator. The build up of the fluence rate in the cavity due to multiple reflections, termed the integrating sphere effect, has been taken into account in the derivation of equations (5) and (7).

3. MATERIALS AND METHODS

3.1. Optical property measurements

The Pockels cell-based photon migration instrument used in these experiments has been described elsewhere[7]. Briefly, light from a continuous wave argon-ion-pumped dye laser (λ = 630 nm) passes through the photon migration instrument, and the resultant pulses are launched into the tissue through a 600 μm dia. silica fiber. A small portion of the light is diverted to a reference photomultiplier tube (PMT) which allows phase and modulation locking of the instrument. Scattered light is collected by a second fiber, identical to the source fiber, and transmitted to the measurement PMT. The total time required to obtain phase and modulation data from 50 frequencies up to 250 MHz is approximately 30 seconds.

Intact uteri were obtained immediately following hysterectomy and placed on ice. Ex vivo measurements were performed on six, cold fresh specimens (1 post- and 5 pre-menopausal). Both frequency domain and steady-state measurements were made in transmittance mode, i.e., source and detector fibers inserted into the tissue and facing each other. In the case of the frequency domain measurements, phase vs. frequency spectra were obtained as a function of source-detector separation by backing the detector fiber away from the source fiber using a micropositioner. In the steady-state measurements, the light beam was steered around the Pockels cell and launched directly into the source fiber. The detector fiber was moved in increments of either 1 or 2 mm and the dc intensity recorded.

3.2. Fluence measurements

The dosimetry model was tested by measuring the light distribution from cylindrical fibers in three different premenopausal human uteri. In all cases, measurements were completed within 4 hours of hysterectomy. Specimens were placed on ice and measurements were initiated within 45 minutes of removal. A cylindrical source fiber was inserted through the cervix and an isotropic detector fiber was inserted through the uterine wall. A hysteroscope was used to visually verify the positioning of the detector fiber with respect to the source fiber. The detector fiber was then retracted in a direction normal to the axis of the cylinder. The exact position was monitored by micrometer readings. The detector fiber was positioned in the endometrial layer over the first 3 to 4 mm, while larger source-detector separations corresponded to placement of the detector fiber in the myometrial layer. The lumen of the uterine cavity was collapsed during the measurements. The dimensions of the cylindrical diffusing fibers were 1.2 mm in diameter and 30 mm in length, and the diameter of the spherical probe was 0.8 mm. The spherical detector fiber was calibrated by immersing the tip into a water-filled cuvette and irradiating with an He-Ne laser beam focused to a spot less than the diameter of the detector tip. For tissue studies, a total of 300 mW (100 mW cm^{-1} diffusing tip) of 630 nm light provided by an argon-ion-pumped dye laser was launched into the 3 cm long cylindrical source fiber.

4. RESULTS AND DISCUSSION

4.1 Optical property measurements

Optical parameters of the human uterus are summarized in Table 1. The optical properties of the bulk uterus were determined by combining the expressions for the penetration depth [equation (2)] and phase velocity [equation (3)].

Table 1. Optical parameters of the uterus

Sample	No. of Samples	Penetration Depth (mm)	Phase Velocity (mm/s) x 10^{10}	μ_a (mm^{-1}) x 10^{-2}	μ'_s (mm^{-1})
Post-menop.	1	2.59 ± 0.26	5.72 ± 0.17	5.15 ± 0.54	0.91 ± 0.17
Pre-menop.	4	4.79 ± 0.32	3.96 ± 0.07	1.93 ± 0.13	0.73 ± 0.09
		3.39 ± 0.28	4.56 ± 0.22	3.14 ± 0.30	0.89 ± 0.15
		5.11 ± 0.20	4.65 ± 0.49	2.13 ± 0.24	0.60 ± 0.08
		4.77 ± 0.45	4.02 ± 0.49	1.97 ± 0.30	0.73 ± 0.15

There appear to be significant differences in penetration depth, phase velocity and absorption coefficient between the two different tissue types. Absorption differences are probably due to differences in water and hemoglobin content[8]. No significant differences in the transport scattering coefficients were observed, although the dense, shrunken post-menopausal uterus had slightly higher μ'_s values than some of the pre-menopausal specimens.

Inter sample variation may be due to differences in stage of the menstrual cycle at which the measurements were made. The uterus is under hormonal control and undergoes significant morphological change (including blood content) during the cycle.

The measurements described here are not suited to the clinic due to their highly invasive nature. In principle, it should be possible to obtain the optical properties of biological tissues, such as the uterus, from simple surface measurements using FDPM. Based on the measured optical properties of the uterus, we estimate that modulation frequencies of up to 500 MHz are required in order to reliably calculate optical properties solely from phase and modulation information[8].

The situation in the uterus is complicated by the fact that it is a layered structure: it is really the optical properties of the thin endometrial layer that is of interest. Unfortunately, the optical properties measured here are more indicative of the underlying thick muscular myometrial layer as most of the measurements were performed there. This was due to difficulties associated with positioning the source and detector fibers in the 3-5 mm thick endometrium.

Noninvasive determination of optical properties in layered structures is difficult, especially in situations where the upper layer is very thin (as for example, in the case of the endometrium). Furthermore, reasonable estimates of optical properties will likely require accurate knowledge of layer thickness. This can be accomplished using ultrasound or MRI. In principle, it should be possible to determine unambiguously the optical properties of the endometrium using GHz modulation frequencies since, at these frequencies, the photon density waves will be confined mostly to the surface layers. Such measurements may be possible using a network analyzer-based FDPM instrument capable of modulation frequencies of up to 3 GHz[9]. In practice however, accurate determination of optical properties from such measurements is difficult due to inaccuracies of diffusion theory at high modulation frequencies.

Alternatively, lower modulation frequencies may be used in combination with more sophisticated layer models. For example, Alexandrakis et al[10] have employed dc and frequency (ca. 200 MHz) measurements to extract the optical properties of a 1.5 mm surface layer to an accuracy of approximately 15 % using a two-layer diffusion model[11]. Better accuracy could not be obtained due to failure of the diffusion approximation at close source-detector separations, i.e., less than 2 mm. Their results also suggest that pure dc measurements cannot yield estimates of the optical properties of the top layer to an accuracy of better than 15 %. More accurate estimates will require the development of better models, such as hybrid Monte Carlo-diffusion theory models.

4.2. Fluence measurements

The correlation between measured and calculated light distributions in a premenopausal uterus is shown in Figure 2. The predicted fluence rate was obtained from equation (5). The good agreement between calculated and measured fluence rates provides preliminary validation of the light distribution model and permits its utilization in human dosimetry applications.

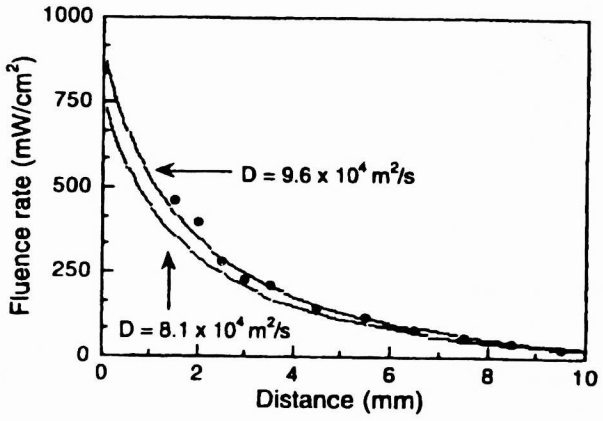

Figure 2. Measured and calculated fluence rates (mW cm^{-2}) from a single cylindrical applicator axis for premenopausal human uteri[2]. The symbols (•) represent the measured data, and the lines represent simulated values using equation (5). measurements and simulations show the response in the midplane of a 1.2 mm diameter, 3 cm long diffusing fiber at 100 mW cm^{-1}, λ = 630 nm, optical penetration depth = 4.4 mm.

Since the cavity of the human uterus is normally collapsed and has a triangular shape, several cylindrical applicators will be required in order to deliver a sufficiently uniform optical dose throughout the uterine cavity. An example of a possible composite applicator consisting of three cylindrical fibers is illustrated in Figure 3. The fibers can be spread out in trifurcation following insertion into the uterine cavity.

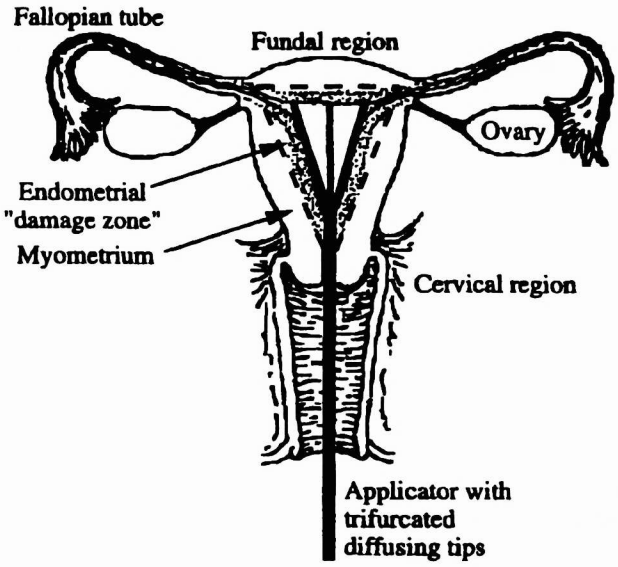

Figure 3. Positioning of a trifurcated applicator in the human uterus.

As expected, calculations show that the minimum fluence rate is found in the upper fundal plane as the distances between the fibers are greatest here and because each fiber may be assumed to act as a semi-infinite long cylinder[2]. Based on our dosimetry model, we have calculated that a satisfactory optical dose of approximately 50 J cm^{-2} can be delivered at a depth of 4 mm in the upper fundal plane in approximately 20 minutes using a trifurcated applicator[2]. This assumes individual applicator lengths and diameters of 40 and 1.2 mm, respectively, and a 14° separation angle between adjacent applicators. The optical power is 100 mW cm^{-1}, the bleaching fluence is 75 J cm^{-2}, and the optical penetration depth and diffusivity are 2.6 mm and 8.1 x 10^{4} $m^{2}s^{-1}$, respectively.

It is important to note that the fluence rate in the critical fundal region can be significantly improved if the uterine walls are separated by a few millimeters. This was experimentally verified in a set-up where all three fibers were radiating. The fluence rate was monitored in the critical region, 2-4 mm from the uterine wall when 3-5 ml of a high-viscosity, optically clear liquid was injected into the uterine cavity. The fluence rate increased typically by a factor of six to ten after the injection. Thus, the fluence rate in the uterine cavity from light scattered back from the uterine wall is a very efficient process[12].

From a clinical point of view, calculation of PDT treatment times based on average optical properties may result in significant dose inaccuracies in individual patients. This is due to significant patient-to-patient variability in optical properties (see Table 1). Furthermore, the fluence rate may change during treatment due to alterations in blood flow. Thus, real-time monitoring of the optical fluence distribution may be necessary in order to achieve sufficient accuracy in the optical dose. This would require the insertion of isotropic fiber detectors into the treatment volume. In practical terms, this would be very difficult to do.

4.3. PDT in the brain

An indwelling balloon applicator which can be used in both brachy and photodynamic therapies has recently been developed (Figure 4)[6]. Measurements of the uniformity of the light distribution surrounding this applicator have been performed in tissue-simulating solutions[5].

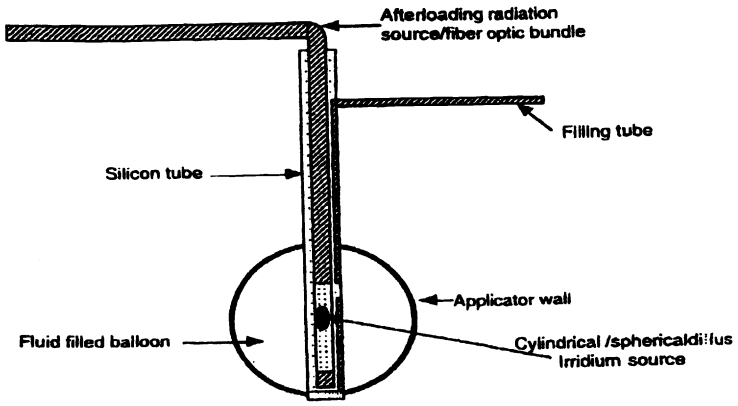

Figure 4. An indwelling balloon applicator for brachy and photodynamic therapy.

Light (λ = 630 nm) from an argon-ion-pumped dye laser was launched into an isotropic fiber which was positioned in the center of the 3 cm dia. balloon applicator containing a 0.1 % Intralipid (Kabivitrum, Inc., Clayton, N.C.) solution. The measured light distribution was uniform to 5 %. Based on a simple spherical geometry [equation (7)] we wanted to know if a sufficient light dose could be given during the 5 – 6 days the patient is hospitalized for the high dose rate brachytherapy treatment. Assuming a source power of 200 mW, optical diffusivity of 5.4 x 10^{4} $m^{2}s^{-1}$ [13] and optical penetration depth of 3.2 mm^{-1} [14], a treatment time of approximately 400 minutes would be required to deliver a dose of 45 J/cm^{2} to a depth of 1 cm in brain

tissue. This calculation is based on average optical property values from the literature. However, significant patient-to-patient variability in optical properties of brain tissue has been observed. For example, Wilson and Muller[14] have measured a four-fold difference in tumor penetration depth in five patients. Furthermore, as discussed previously, optical properties may change during treatment due to changes in blood flow and/or to edema. Again, this would suggest a very important role for real-time monitoring of optical fluence distributions during PDT. This would be particularly difficult in this case due to the possible complications associated with the insertion of optical fiber detectors into the brain. In practical terms, it would be difficult due to the small diameter of the burr hole – it is just large enough to accommodate the applicator which remains in place during the 5 – 6 day treatment period. A possible solution may be to monitor the progress of PDT treatment using magnetic resonance imaging (MRI)[15]. The applicator is initially positioned in the resection cavity using interventional MRI, and verification of applicator position is performed throughout the treatment period using either MRI or computed tomography (CT). The appeal of using MRI is that it might be used to determine the depth of the immediate PDT effect, which could be correlated with tissue necrosis[16].

5. CONCLUSIONS

There are numerous challenges associated with accurate optical dosimetry in PDT. In principle, the optical fluence distribution can be determined from knowledge of the optical properties of the irradiated tissue. However, measurement of tissue optical properties is difficult and may require complicated models for interpretation. Much of the optical property data from humans have come from ex vivo measurements in bulk tissue (e.g. the uterus measurements described here), or from direct measurements on thin frozen tissue sections. Such ex vivo measurements are problematic in that they do not reflect the true in vivo environment. For example, significant differences between in vivo and ex vivo tissue hydration and vascularity are likely to result in optical property differences. Only a few in vivo measurements have been attempted in humans. Unfortunately, the limited data show significant patient-to-patient variability in optical properties. This suggests that significant dose inaccuracies may result if average optical property values are used to plan a PDT treatment. A possible solution is direct monitoring of fluence distributions during treatment using optical fiber probes. Such real-time monitoring could also detect fluence rate changes due to alterations in blood flow during treatment. In practical terms, these measurements are difficult and time-consuming; many physicians would undoubtedly opt to forgo such measurements.

This paper has addressed only issues related to optical dosimetry in PDT. However, in addition to the optical dose, the overall efficacy of PDT depends in a complex way on factors such as the kinetics of drug uptake, type of drug, cellular localization and tissue oxygenation status. Due to the difficulties associated with measuring these variables, alternative methods have been proposed to monitor the overall efficacy of PDT. One such scheme involves the direct monitoring of the infrared (1270 nm) luminescence associated with the singlet-to-triplet de-excitation of molecular oxygen[17]. This may be possible in the near future with the development of near-infra-red detectors of high sensitivity and low noise[16]. Alternatively, it may be possible to use photosensitizer photobleaching as an index of effective delivered dose[16]. Ideally, a technique which could monitor tissue changes directly is desirable. Such photobiological dosimetry may be possible using quantitative radiological imaging such as MRI and CT.

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