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PHOTODYNAMIC THERAPY DOSIMETRY

A Task Group Report of the General Medical Physics Committee of the Science Council

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CONTENTS

A. INTRODUCTION

A1. What is PDT?

Photodynamic therapy (PDT) is a light-activated chemotherapy in which light is used to activate a photosensitive drug that has accumulated within cells such that it causes oxidative injury to the cells. Unlike traditional chemotherapy, which has a systemic effect, PDT achieves a localized effect. In this sense, PDT is more like a surgical or radiation therapy technique than a chemotherapeutic treatment.

The basic ingredients for a successful PDT treatment are: (1) drug, (2) light, and (3) oxygen. As shown in Figure 1a, the photosensitive drug is activated by absorbing a photon to achieve its activated state. The activated drug then reacts with molecular oxygen dissolved in the cellular interior to create radical oxidizing species, usually singlet oxygen. The oxidizing radical then attacks structures of the cell via an oxidation mechanism to cause injury. Such injury may lead to cell death via coagulative necrosis or via apoptosis, depending on the choice of photosensitizing drug and the amount of drug and light administered.

PDT is a light-activated chemotherapy. A photon is absorbed by a photosensitive drug that moves the drug into an excited state (see Figure 1b). The excited drug can then pass its energy to oxygen to create a chemical radical called "singlet oxygen." Singlet oxygen attacks cellular structures by oxidation. Such oxidative damage might be oxidation of cell membranes or proteins. When the accumulation of oxidative damage exceeds a threshold level, the cell begins to die.

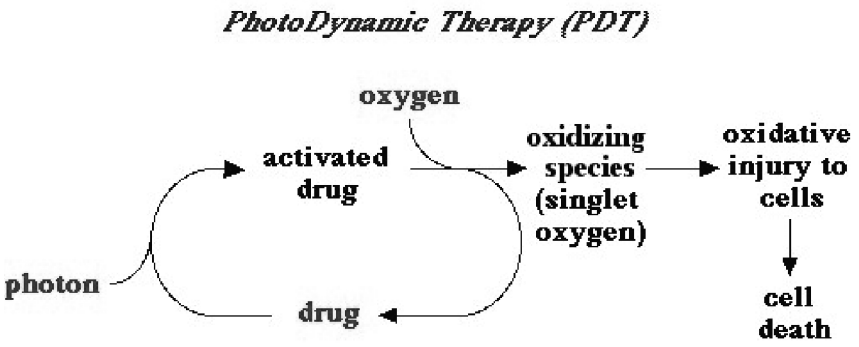

Figure 1a. Photon + drug + oxygen → oxidizing radical → oxidative injury → cell death.

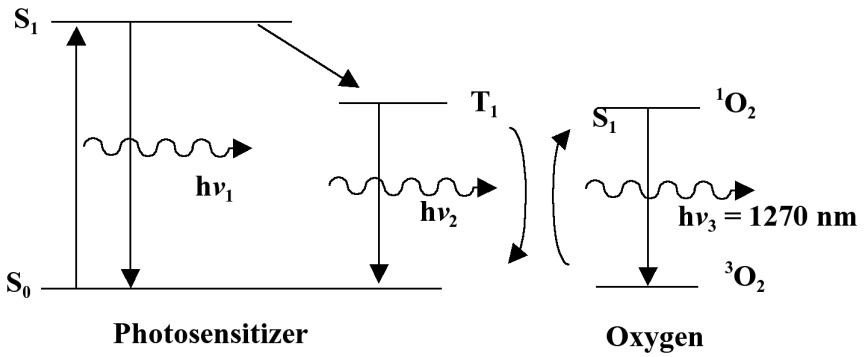

Figure 1b. The production of singlet oxygen from a photosensitizer.

A2. Current Clinical Status of PDT

PDT has begun to find approved uses in medicine. In 1996, the FDA approved PDT (Photofrin™) for palliative treatment of obstructive esophageal cancer. In 1998, the FDA approved PDT (Photofrin™) for treatment of certain esophageal and obstructive lung cancers. In 2000, the FDA has approved PDT (Verdiporfrin™, benzoporphyrin derivative) for treatment of macular degeneration of the retina associated with old age. A variety of other applications are in clinical trials, including treatment of prostate cancer, head & neck cancer, skin cancer, pleural cancer, intraperitoneal cancer, and treatment of the resection bed after brain tumor surgical excision.

A3. Current Status of Optical Dosimetry

The dosimetry for treating a thin superficial cancer differs from the dosimetry for treating a bulky tumor. In the first case of a thin superficial cancer, the light is delivered to the surface cancer directly with some contribution from backscattered light reflected toward the surface by the underlying tissues. In the second case of a thick tumor, the light must penetrate into the tissue to reach a desired depth of treatment. The following discussion will first consider the dosimetry of the thin superficial cancer, then consider the thick tumor.

Thin Superficial Cancer (<100 microns)

A thin superficial cancer (the thin layer is defined due to the mean free path of the photon being significantly greater than the thickness of a tumor) directly receives the incident treatment light as well as backscattered light reflected from the underlying tissues. Because the cancer is thin, on the order of hundreds of microns in thickness, the cancer receives about the same amount of light throughout its volume. Light penetration through the cancer is not an

issue. Hence a discussion of dosimetry for a thin superficial cancer is a good introduction to the basics of PDT dosimetry.

Consider that there is a threshold concentration (R_{th} [M]) of oxidizing events that needs to occur in a sensitive location within a cancer cell to elicit the cascade toward cell death.

$$R_{th} = E\, k_s\, T\, b\, \varepsilon\, D\, \Phi\, f, \tag{1}$$

where

- R_{th} is the concentration [M] of oxidizing radicals that attack a sensitive cellular site,
- E is the irradiance on the tissue surface [W/cm^2] (broad beam one-dimensional model),
- k_s is the backscatter factor due to reflected light from underlying tissue,
- T is the exposure time of treatment light [s],
- b is conversion factor λ/hc [ph/J] (λ is wavelength, h is Planck's constant, c is speed of light),
- ε is extinction coefficient of photosensitive drug [cm^{-1} M^{-1}],
- D is the concentration of the photosensitive drug [M],
- Φ is the quantum yield for conversion of activated drug to oxidizing radicals, which usually depends on the oxygen concentration dissolved in the cells,
- f is the fraction of generated oxidizing radicals, which attack the sensitive cellular site, while the fraction $(1 - f)$ of the radicals attack lesser sites and have minor effect.

One can separate these quantities into three categories: light dosimetry quantities (E, k_s, T, b, ε), drug concentration (D), and photobiological quantities (Φ and f). The light dosimetry quantities determine the total light absorbed by the photosensitizer drug. Significant advances have been made to determine the light dosimetry quantities accurately and *in vivo*. This is the quantity of most concern to medical physicists. The drug concentration determines the amount of useable drug reaching the target. Significant development has been made in this area to determine the drug concentration using absorption or fluorescence measurements *in vivo*. Since both quantities can be used to determine *in vivo,* the concept of threshold dose (D_{th}) can be introduced to characterize the light absorbed by the photosensitizer drug. One may hypothesize that when the light dose exceeds the threshold dose, D_{th}, complete tumor necrosis happens, provided ample oxygen supplies exist. The last quantity concerns not only the quantum efficiency of the photosensitizer drug but also the production of singlet oxygen. This quantity is a function of oxygenation and is not well understood currently.

In practice, the values of only some of these parameters are known for a specific tissue type and specific photosensitizing drug. In particular, it is difficult to know R_{th}, f, and Φ. The light (E), backscatter (k_s), exposure time (T), and concentration (D) can be determined experimentally at the time of a treatment. In principle, one should be able to determine all the light dosimetry quantities. But in usual practice, only the light delivered (E) and the exposure time (T) are controlled in a treatment. In other words, the physician must ensure the dose of light is adequate:

$$ET > \text{constant} = R_{th}/k_s\ b\ \varepsilon\ D\ \Phi f. \tag{2a}$$

The physician may ignore that the backscatter (k_s) can vary with changes in tissue optical properties; for example, as the tissue becomes inflamed with blood, which reduces reflectance. In general, k_s can range from 1.0 to 4.0 for various tissues with a value of 1.5 to 3.0 being typical.

Recent advances have made it possible to determine both fluence rate and drug concentration *in vivo* accurately. As a result, equation (2) can also be modified to

$$k_s\ b\ \varepsilon\ D\ ET > \text{constant} = R_{th}/\Phi f. \tag{2b}$$

The constant ($R_{th}/\Phi f$) is also called "threshold dose" (Patterson, Wilson, and Graff 1990; Farrell et al. 1998). Originally, the threshold dose was defined as dose (energy per unit volume) absorbed by drug, $eDksET = eDF_0T$, where F_0 is the fluence rate. Wilson and Patterson have found this quantity to be a constant to predict necrosis for a wide range of light fluence rate and drug concentration. This is later modified as number of photons absorbed by drug per unit volume, $beDF_0T$, so that the resulting constant becomes wavelength independent.

The physician may ignore that the concentration of photosensitizing drug (D) in the tissue can vary from patient to patient, or site to site. A certain drug dose is delivered to the patient (D_0 [g/kg.b.w.]) but individual pharmacokinetics and drug distribution determine the final concentration D. For example, in esophageal cancer the drug concentration D is varying about $\pm 50\%$.

The physician may ignore how the oxygen concentration in the tissue varies, which affects the value of the quantum yield (Φ) for oxidizing radicals. Not only can the oxygen levels in a tissue vary, for example if the tissue is poorly vascularized, but also the PDT itself consumes oxygen and can deplete tissue oxygen if too high a rate of treatment is used, i.e., if the product $(E)(D)$ is too high.

Presently, the physician must ignore any variations in how oxidizing radicals attack the cells and assume that the threshold concentration of generated radi-

cals (R_{th}/f) for cell killing is constant. The magnitude of such variability has not yet been established for most cancers with most photosensitizing drugs.

For treatment of thin superficial cancers, the physician must ensure that the product ET exceeds a constant value that has been determined by prior clinical trials. This constant is presumably well above the threshold constant value so as to ensure that most cancers are treated despite the above cited variations. However, PDT dosimetry certainly is at an early stage of development.

It is important for the medical physicist, who assists in a PDT procedure by specifying the irradiance E and the exposure time T, to be confident of the calibration of the light source and the timing system. From a legal point of view as well, this task is very important. Yet, the general public should know that the potential variations in the many factors that affect PDT can easily exceed a minor 10% to 20% error in light dosimetry. In the future, optical feedback measurements will be able to document many of the dosimetry factors (D,Φ) currently ignored. Also, our understanding of the process of oxidative attack in cells will improve (f, R_{th}).

Thick Tumor

In a thick tumor, such as an obstructing esophageal cancer or bronchial cancer, the dosimetry for treatment of the tumor surface where treatment light is administered is the same as that described above for the thin superficial tumor. However, treating just the surface of the tumor is not the goal in such cases. The goal is to treat the tumor to some desired depth, whether for palliation or for cure. The following discussion describes the dosimetry of treating to a desired depth.

The expression that describes the maximum depth of necrosis, $z_{necrosis}$, is similar to equation (1) but with a more general term H_0 for fluence rate: [The expression equation (3) is only true for uniform collimated light irradiation and is not generally true for other light source geometry. Since interstitial light delivery should be used and will become common for treatment of thick tumor (ref., uniform irradiation for thick tumor in head & neck failed miserably due to limited light penetration, 8th IPA World Congress of Photodynamic Medicine, June 5–9, 2001, Vancouver, Canada), one should use fluence rate rather than irradiance for thick tumors.]

$$R_{th} = H_0(z)\, T\, b\, \varepsilon\, D\, \Phi\, f, \tag{3a}$$

where

$$H_0\left(z, r, \text{or } \rho\right) = \begin{cases} E \cdot k_s \cdot e^{-z_{necrosis}/\delta} & \text{parallel beam} \\ E \cdot k_s \cdot e^{-r_{necrosis}/\delta} / r & \text{spherical beam} \\ E \cdot k_s \cdot e^{-\rho_{necrosis}/\delta} / \sqrt{\rho} & \text{cylindrical beam} \end{cases}, \tag{3b}$$

where

δ is the effective optical penetration depth for which light attenuates to 1/e or 37% of its value,

$H_0(z, r,$ or $\rho)$ is the fluence rate in tissue at position z (depth from irradiated surface), r (radius from the spherical irradiation center), or ρ (center radius from cylindrical irradiation axis), respectively.

Φ is, as previously defined, quantum yield.

For example, rearrangement of equation (3) for parallel beam yields a prediction of the maximum depth of necrosis, $z_{necrosis}$:

$$z_{necrosis} = \delta \ln(E\, k_s\, T\, b\, \varepsilon\, D\, \Phi\, f/R_{th}). \quad (4)$$

The depth of necrosis due to PDT treatment is linearly proportional to the optical penetration depth δ, but proportional to the natural logarithm of all other factors. In other words, one could double the depth of treatment by choosing a wavelength of light that doubled the optical penetration δ. However, one would have to change any other parameter 7.4-fold to double the treatment depth.

Importance of Proper Optical Dosimetry

The primary requirement is to ensure sufficient light such that the product of irradiance and exposure time exceeds the threshold for effect, $ET >$ constant as in equation (2). Because this is a linear relationship, a slight deficiency in light dose may fail to achieve treatment. More work is needed on the variability of this threshold in tissues. However, it should be assumed that the Food and Drug Administration (FDA)-approved dose has a safety margin based on the statistics of clinical trials. Nevertheless, the obligation to verify and ensure the correct light dose is professionally, ethically, and legally binding. However, if there is a failure in treatment, the general public should be aware that at this early stage of PDT dosimetry development there are a variety of reasons why a treatment might fail which are not due to improper light dosimetry.

In the future, we anticipate the development of optical feedback measurements to quantify many of the variables on an individual patient and on an individual treatment site basis. We anticipate a better understanding of the variability in tissue sensitivity to a standard PDT protocol. In the future, a cocktail of photosensitizing drugs may be used in PDT to better ensure a reliable standard effect. Just as radiation therapy took decades to develop its dosimetry tools, PDT will take a few years to optimize its dosimetry. Fortunately, PDT in its current state still affords a desirable treatment modality with good results and little risk.

A4. Implications of Inappropriate Dosimetry on the Therapy

The consequences of inappropriate PDT dosimetry are perhaps modest compared to a mistake in chemotherapy or radiation therapy. PDT is a local treatment so there is only a limited effect if an inadvertent overexposure occurs. Moreover, the treatment zone is proportional to $\ln(ET)$, so a major overtreatment with light causes a minor change in the treatment depth. More important is the consequence of undertreatment with light. Failure to exceed the required threshold of effect will result in no effective treatment. Such a failure causes undue stress, time, and expense for the patient and the hospital staff and may lead to mistaken conclusions as to the sensitivity of a tumor to PDT that might affect subsequent clinical decisions. These are serious consequences, but not direct physiological consequences. PDT can be repeated many times, unlike radiation therapy, which has an upper limit. So if a failed treatment is recognized as a dosimetry problem, the treatment can be repeated.

A5. Purpose of the Writing

The purpose of this report is to provide a reference guide for the medical physicist responsible for light dosimetry during PDT treatments. By outlining the issues involved in PDT dosimetry, it is hoped that future work is stimulated to specify the many key factors that are not yet controlled during PDT. The report also speaks to the general public regarding what is known and not known about PDT dosimetry and thereby instructs as to both the importance and the limits of optical dosimetry with respect to variation in treatment outcomes.

A6. Structure of the Writing

This report presents a complete definition of terms used in PDT dosimetry. Calibration techniques during preventative maintenance of laser sources are discussed. Dosimetry procedures at the time of PDT treatment are described. Training for the physicist, nurse, and physician involved in PDT treatments is outlined. Also presented is a recommendation as to the fundamental information that should be included in journal articles so as to enable a reader to evaluate the dosimetry associated with the reported PDT effects.

A7. Disclaimer

This AAPM report is the best effort compilation of a group of investigators currently working in the field of PDT. This report does not warrant that its guidelines will guarantee a successful treatment outcome and avoidance of complications.

B. DEFINITION OF TERMS

In this section we define terms that are commonly used in PDT physics and dosimetry. The definitions and symbols are consistent with an earlier document, AAPM Report No. 57, Recommended Nomenclature for Physical Quantities in Medical Applications of Light (AAPM 1996).

B1. Fundamental Quantities Describing the Light Field

Radiant energy (Q): Total energy emitted, transferred, or received as electromagnetic radiation. SI unit is J.

Radiant power (P): Power emitted, transferred, or received as electromagnetic radiation. SI unit is W.

Energy radiance (L): Radiant power transported at a given field point in a given direction per unit solid angle per unit area perpendicular to that direction. The SI unit is W m^{-2} sr^{-1}. The radiance provides a complete description of the light field and is the fundamental quantity in the radiative transport equation. While important from a theoretical standpoint it is rarely measured directly.

Energy fluence rate (E_0): Ratio of total power incident on an infinitesimal sphere (containing the point of interest) to the cross-sectional area of that sphere. It can also be defined as the integral of the radiance over 4π solid angle. The SI unit is W m^{-2}, although the unit mW cm^{-2} is still more common in PDT. The fluence rate is the fundamental parameter in PDT dosimetry as it determines the local interaction rate of photons. It can be measured using a specialized detector that has an isotropic response.

Energy fluence (H_0): Total radiant energy incident on an infinitesimal sphere (containing the point of interest) divided by the cross-sectional area of that sphere. SI unit is J m^{-2} but the unit J cm^{-2} is common in PDT. Obviously, the fluence is the time integral of the fluence rate.

Irradiance (E): Radiant power incident on an infinitesimal surface element (containing the point of interest) divided by the area of that element. The SI unit is W m^{-2} but the unit mW cm^{-2} is commonly used in PDT. Note that the irradiance and the fluence rate have the same physical units (power per unit area) but they are not the same quantity. The irradiance is defined for a particular surface whereas the fluence rate can be defined and measured in free space or the interior of an object. Terms such as power density, flux density, and intensity, which have been used to describe the irradiance, should be avoided.

Radiant exposure (H): Radiant energy incident on an infinitesimal surface element (containing the point of interest) divided by the area of that element. The SI unit is J m^{-2} but, in PDT, the unit J cm^{-2} is more common. The radiant exposure is the time integral of the irradiance. The term "energy density" which has been applied to this quantity should be avoided. The radiant exposure is specified for PDT treatments using surface irradiation.

B2. Quantities Describing the Target Tissue

Absorption coefficient (μ_a): The probability that a photon will be absorbed on traversing an infinitesimal distance in tissue divided by that distance. In other words, the probability of absorption on traversing an infinitesimal distance dx is $\mu_a\, dx$. The SI units are m^{-1} but cm^{-1} or mm^{-1} are more commonly employed in PDT.

Scattering coefficient (μ_s): The probability that a photon will be scattered on traversing an infinitesimal distance dx is $\mu_s\, dx$. SI units are m^{-1}.

Total attenuation coefficient (μ_t): Sum of the absorption and scattering coefficients. SI units are m^{-1}.

Phase function $p\left(\hat{\Omega}, \hat{\Omega}'\right)$: Probability density function describing the angular dependence of light scattering.

Anisotropy parameter (g): Average cosine of the scattering angle. For isotropic scattering $g = 0$. In most soft tissues scattering is forward peaked with $g > 0.9$.

Transport scattering coefficient (μ'_s): Also referred to as the reduced scattering coefficient μ'_s is an effective isotropic scattering coefficient given by $\mu'_s = (1 - g)\, \mu_s$.

Mean free path (mfp): The mean distance between photon interactions, given by $1/\mu_t$. The SI unit is m.

Effective attenuation coefficient (μ_{eff}): Under many irradiation conditions the fluence rate decreases exponentially with distance from the source if measurements are made sufficiently far from the source and tissue boundaries. In this regime $H_0 \mu \exp(-\mu_{eff}\, r)$ where μ_{eff} is the effective attenuation coefficient and r is distance. SI unit is m^{-1} although mm^{-1} or cm^{-1} are commonly used in PDT. For soft tissues in the PDT wavelength range $\mu_{eff} \sim 1\ mm^{-1}$.

Optical Penetration depth (δ): Also referred to as the diffusion length, this is the reciprocal of μ_{eff}.

B3. Terms Associated with the Light Source

Continuous wave (cw): A source that emits light continuously. Examples applicable to PDT are diode lasers, light-emitting diodes (LEDs), lamps, and argon-pumped dye lasers.

Pulsed: A source which emits light as a series of pulses, for example, a dye laser pumped by a frequency-doubled Nd:YAG laser. Pulsed sources are characterized by their pulse repetition frequency [in hertz (Hz)], the pulse width (definition may vary), the pulse energy [typically in millijoules (mJ)], the peak power within a pulse [in watts (W)], and the average power (in W). If the pulse energy is low enough, a pulsed source will produce the same biological PDT effect as a cw source with the same average power.

Broadband: A source with a wide spectral output compared to typical laser linewidths.

Tunable: A source whose output wavelength may be adjusted—typically over a range of tens of nanometers.

Bandwidth: A term used to characterize the width of the source's output spectrum. A variety of definitions are used in practice. For example, the bandwidth of a laser source could be quoted as the wavelength range over which the power is greater than 50% of the power at the peak wavelength.

B4. Terms Associated with Light Delivery

Superficial treatment or irradiation: A PDT treatment where the goal is to irradiate an internal or external tissue surface. This may be accomplished with optical fiber delivery or, in the case of external surfaces, lamp or LED sources may be used directly.

Interstitial or implant treatment: A PDT treatment designed to treat a volume of tissue by implanting suitable optical fibers in the interior of the target volume.

Intralumenal treatment: A PDT treatment designed to irradiate all, or a portion of, the interior surface of a cylinder such as the lumen of the esophagus.

Intracavitary treatment: A PDT treatment designed to irradiate all, or a portion of, the interior surface of a sphere, such as the wall of the bladder.

Flat-cut (cut-end) fiber: An optical fiber with a simple cleaved end. Such a fiber produces a non-uniform output and is not optimal for surface irradiation.

Energy radiance detector: Angled flat-cut fiber used to measure energy radiance directly.

Microlens fiber: A fiber with a microlens in close proximity to the cleaved end. This design produces a uniform circular field at a convenient distance from the fiber, and is often used for surface irradiation.

Isotropic diffuser fiber: A fiber designed for intracavitary use, consisting of a small volume of scattering material at the fiber tip. Ideally, such a fiber acts as a point source of illumination.

Linear diffuser: An optical fiber modified to emit light along some portion of its length. The "active" length may be several centimeters. Such fibers are used in intralumenal treatments and may also be made robust enough for interstitial implants.

Light dose (dose rate): An imprecise term used to describe light delivery during PDT. For surface illumination this corresponds to the rigorously defined exposure in section B.1 (units J cm^{-2}). For linear diffusers, the light dose is quoted in terms of energy delivered per unit length (J cm^{-1}). For point sources it is given simply as total delivered energy (J). Note that this term describes the energy delivered to the tissue—it does not give the actual fluence at any point in the tissue.

Isotropic detector: An optical fiber with approximately isotropic response which, when properly calibrated, can be used for direct measurements of fluence or fluence rate.

Coupling efficiency or transmission efficiency: The ratio of power delivered by the treatment fiber to the source power, usually expressed as percent. Losses may be due to reflection, attenuation, or geometrical factors.

Beam splitter: A device designed to divide optical power into two or more paths. In PDT a beam splitter allows two or more fibers to be coupled to a single source, usually for interstitial treatments.

Optical filters: Optical devices used to alter the power or spectral character of light. Neutral density filters provide attenuation, which is independent of wavelength. Bandpass filters transmit light over a narrow bandwidth. Notch filters attenuate light over a narrow bandwidth. Cut-on filters transmit light above a specified wavelength. Cut-off filters attenuate light above a specified wavelength.

C. CALIBRATION STANDARD/PROCEDURE FOR PDT DOSIMETRY

C1. Calibration During Preventative Maintenance

Light Source (Weekly)

Absolute output from light source within equals $\pm 10\%$ to an optical power meter traceable to the National Institute of Standards and Technology (NIST) standard. While there is no dispute that the power meter can be calibrated to within 5% to NIST standard, it is hard to calibrate the *in vivo* photodiodes with the same precision, due to its wavelength effect, its nonlinearity, and its angular dependence. $\pm 10\%$ is probably achievable with effort. $\pm 15\%$ is easily achievable by most physicists.

Light Source Stability

Uncertainty in integrated energy due to fluctuation of light source stability should be less than 5%/hour.

Light Source Wavelength

a. Tunable laser: Peak wavelength within 2 nm of target drug absorption wavelength.
b. Broadband light source (including diode lasers): >90% integrated spectral overlay between source and drug.
c. Diode laser: Laser source generated by laser diodes. These laser sources usually have shorter coherent length and larger bandwidth (~5 nm) but are becoming more popular because of their ease of use and long lifetime. It is also relatively easy to modulate the light source by simple power modulation.

d. LED: Light-emitting diodes usually generate noncoherent and narrow-band (or broadband) light. These light sources usually have low power but are very inexpensive.

Power Meter

Calibrated against a NIST standard every one year. There are three types of power meters: thermocouple, photodiode, and piezoelectric detector. The thermocouple power meter has very little wavelength dependence and can determine laser power absolutely, however, it is slow to response to power change. This type of detector is most suitable for absolute calibration. The photodiode has strong wavelength dependence and responds quickly to output changes. This type of power meter can be made very small and is suitable for *in vivo* light dosimetry. The piezoelectric detector has fast response and is thus suitable for pulsed radiation.

Timer

Treatment timer accuracy should be within 1%.

C2. Physics Procedure Performed at the Time of a PDT Treatment

NOTE: As available (with development) in situ *dosimetry/monitoring is recommended.*

Light Delivery System Output

The output from light source shall be measured before and immediately after a PDT light irradiation treatment using a certified power meter as described in section C1. Variation in source output at any time during an irradiation, if measurable, should be less than 10% from the initial value based on dosimetry calculation.

Fiber Efficiency

a. Coupling/transmission loss of energy for an optical fiber used in a PDT treatment should be less than 30%.
b. There should be no visual indication of fiber light leakage (mechanical breakage of the fiber).

Treatment Timing

a. Treatment time should be accurate within 1% or 5 seconds, whichever is less, of the prescribed time.
b. A secondary timer is recommended.

Field Size

For a circular superficial irradiation field, the diameter of the field size measured directly at the target surface should be accurate within 10% or 3 mm, whichever is less, of the prescribed treatment field size. Care should be exercised that, when adjacent fields are to be irradiated, there should be no physical overlapping of the fields at the irradiated surface.

Post Treatment Calibration and Documentation

The irradiation irradiant power should be recalibrated after each treatment procedure to assure that no changes have occurred during a treatment. The procedure should include both visual examination of the light-delivering device, i.e., optical fiber, for its physical integrity and an optical measurement of the irradiant power. The post-treatment irradiant power should be within $\pm 10\%$ of its initial setting. Deviations should be noted in the treatment documentation together with possible causes.

Any PDT treatment should be documented for both the physicist and physician. The document should include, but not limited to, the following information:

a. General Information: Patient name, gender, weight, date of treatment, and contact information of the physician.
b. Photosensitizer: Type, amount, route, and time administered.
c. Light treatment: Laser used (serial number), wavelength, prescribed light dose(s), which include both energy fluence rate and energy fluence, treatment site(s), duration of irradiation(s), and post treatment recalibration of the above parameters.

D. TRAINING FOR PHYSICIAN/NURSE/PHYSICIST INVOLVED IN PDT (Minimum Qualification/Training/Credential Required for Physician/Nurse/Physicist To Participate in a PDT Procedure)

D1. Physician

The physician must be qualified by training and experience in the traditional treatment of the specific type of lesion to be treated. For example, for the possible treatment of a prostate lesion with PDT the likely training would be in urology and/or radiation oncology, and for an esophageal lesion either a gastroenterologist or radiation oncologist. In addition, the physician should have completed a course in PDT that covered the topics of fundamental PDT chemistry and biology, PDT physics and dosimetry, and clinical applications of PDT. Such courses are offered in conjunction with several national meetings such as the International Society of Optical Engineering (SPIE), the American Society of Laser Medicine and Surgery (ASLMS), and the American Physical Society

(APS). Alternatively, a physician may be mentored in a particular area of PDT by another physician who is skilled in that clinical area.

D2. Nurse

For nursing professionals participating in a PDT treatment there are several training options. First, they may receive the necessary training directly from another skilled professional such as a trained physician or physicist. In addition to the proper training on patient photosensitivity they will require training on the proper handling of the light delivery system (e.g., Fiber optics, catheters, etc.) as well as the light source (if necessary). Alternatively, they may participate in the same training courses designed for the physicians as mentioned above or in specialized courses for nursing professionals offered at many of the same meetings.

D3. Physicist

A physicist may receive the necessary training in PDT at several of the above-mentioned courses. She/he must demonstrate the necessary skills to make the required dosimetry calculations as well as the required instrument calibrations. Prior training in aspects of radiological physics is useful but not necessary. Alternatively, the physicist may be mentored by another physicist who is skilled in the necessary aspects of PDT physics.

Documentation of the training of all professionals should be provided to the appropriate official responsible for credentialing at her/his facility. Such documentation should consist of a certificate of course completion or a letter certifying the training, signed by the person providing the training. In this latter case, sufficient documentation of the skills/credentials related to PDT of the individual providing the training must also be provided.

D4. Laser Specialist

In some large centers with a large PDT program, it is necessary to have a specialist in charge of maintaining all light sources and light delivery devices. The laser specialist is responsible for routine maintenance of the laser sources, routine output power calibration, and quality assurance (QA) of light delivery devices, and often serves as laser safety officer.

D5. Light Dosimetrist

In centers where routine real-time *in vivo* light dosimetry is performed in complicated applications of PDT, such as intraperitoneal PDT, prostate PDT, or pleural PDT, it may be necessary to have a person in charge of this particular duty. The light dosimetrist is responsible for performing routine *in vivo* light

dosimetry, repair of photodiodes and other dosimetry equipment, and routine QA of dosimeter calibration to ensure a high accuracy of light dosimetry.

E. RECOMMENDATION OF FUNDAMENTAL INFORMATION FOR JOURNALS TO EVALUATE PDT-RELATED ARTICLES/REPORTS

E1. Introduction

PDT is a complicated treatment modality for cancer and proliferative disorders. Briefly, a drug that can be activated by light of a given wavelength is given orally or by injection. The drug becomes concentrated in the target proliferative tissue and, following the application of light, energy is released in one of a number of forms into the surrounding tissue, which leads to cell death.

There are a number of photosensitive drugs and different ways of activating them; the most commonly used combination is a photoporphyrin and a laser.

As with all scientific work, it is important for any worker reading published data in this area to be able to repeat the work. There are no published standards for PDT papers and this section is intended to act as a guide for publication.

Briefly, there are a large number of parameters involved in PDT and these can be split into two groups: those which can be quantified and those which cannot.

E2. Parameters That Can Be Quantified

Light source: State whether laser or non-laser

- Manufacturer: Full details of manufacturer and/or supplier
- Wavelength: Specific wavelength in nanometers for lasers, full width at half maximum (FWHM) range for polychromatic light sources
- Pulsed/CW/quasi CW: If the source is a laser, it must be made clear whether or not the laser is truly pulsed with a high peak pulse power or whether the light is delivered in short bursts from a continuous wave source
- Power output: The power output of the light source should be stated in watts. If a laser is pulsed, then the peak pulse power should also be given
- Calibration: Methods used to verify output at the laser head or other light source
- Stability: Full details of the stability of the source
- Optical coupling: Method by which the light is coupled from the source to the top end of the delivery system

Delivery System

- Manufacturer
- Optical coupling

- Fiber type
- Fiber diameter
- Fiber mechanical properties
- Fiber transmission
- Coating and cladding
- Homogeneity
- Fiber tip
- Diffusers
- Angle of divergence

Light Dosimetry

- Power/energy meter
  - Manufacturer
  - Type
  - Tolerance
  - Accuracy
  - Precision
  - Temporal response
  - National standards
- Sensors
  - Specify type
- Fluence rate
  - At delivery device
  - In tissue
- Integrated fluence
  - At delivery device
  - In tissue
- Irradiance
  - At target tissue

Drug (if commercially available, state commercial name and supplier)

- Molecule
- Solvent
- Level of purity
- Concentration and subsequent dilution
- Delivery: IV/IA/Oral, duration, infusion rate
- Delivery vehicle: adsorbed onto lipids, etc.
- Extinction spectra in solution and *in vivo*
- Quantum yield
- Photobleaching
- Time between delivery and treatment
- Fractionated or single bolus dose regime
- Whole patient photosensitization

Drug Dosimetry (Pharmacokinetics of Drug)

- Serum
- Tissue
- Location in tissue

Tissue (Experimental System)

- Tissue culture
  - Exact description of standard cell culture
    - Cell line
    - Medium, buffer
    - Temperature
    - Concentration of CO_2
    - Incubation parameters
- Animal experiments
  - Species
  - Strain
  - Housing, age, gender
  - Target tissue
  - Tumor line: how administered and maintained
  - Nonmalignant tissue

E3. Parameters That Cannot Be Quantified

Human Disease

The only way of quantifying human disease and patient details is by including full details of the following parameters. Only by amassing a statistically significant cohort of patients can quantification of disease and its response to treatment be achieved. This should normally be by randomized controlled trial.

Tumors

- Histopathology
- Grading
- Tumor size
- Staging

Patient Parameters

- Age
- Sex
- General debility

Previous Treatment

- Surgery
- Radiotherapy
- Chemotherapy

APPENDIX: BASICS OF PDT

As illustrated in Figure 1a (repeated here as Figure A1), PDT depends on the amount of light delivered (L), the amount of photosensitizing drug (D) in the tissue, and the amount of oxygen (O_2) in the tissue. Absorption of light converts D into an activated drug (D^*). Reaction of D^* with oxygen yields oxidizing radicals (R^*, primarily singlet oxygen). A fraction (f) of these radicals attacks critical sites within the cell causing an accumulated oxidative damage (A). When the accumulated damage exceeds a threshold, $A > A_{th}$, then cell death occurs.

The light provided by a delivered fluence rate (ϕ) can be expressed in units of photon concentration:

$$L = \frac{\phi}{c}\frac{\lambda}{hc}\frac{1000}{6\times10^{23}}, \quad [\text{moles/liter}], \tag{A.1}$$

where

ϕ is the fluence rate of light [W/cm^2] or [J/(cm^2 s)],

λ/hc is number of photons per J of energy [ph/J],

λ is the photon wavelength in [cm],

c is the speed of light, 3.0×10^{10} [cm/s],

h is Planck's constant, 6.6×10^{-34} [J s],

there are 1000 cm^3 per liter,

there are 6×10^{23} photons per mole of photons.

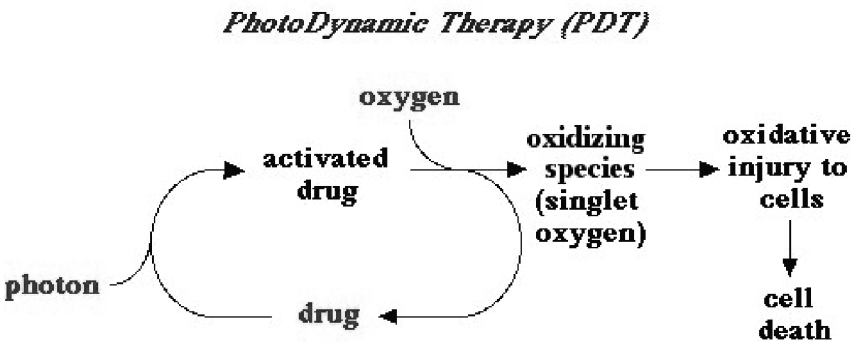

Figure A1. Photon + drug + oxygen → oxidizing radical → oxidative injury → cell death.

The rate constant (k_1) for drug activation (D $\rightarrow$ D*) is:

$$k_1 = c\varepsilon \quad \left[s^{-1} \left(\text{moles/liter} \right)^{-1} \right], \tag{A.2}$$

where

c is the speed of light [cm/s],

ε is the extinction coefficient of the photosensitizing drug [(cm^{-1})/(moles/liter)].

The rate of production of activated drug is:

$$k_1 LD \quad \left[\left(\text{moles/liter} \right) s^{-1} \right]. \tag{A.3}$$

The total amount of activated drug (D^*) produced per unit volume of tissue is:

$$D^* = k_1 LDT = \varepsilon \phi DT \frac{\lambda}{hc} \frac{1000}{6 \times 10^{23}} \quad \left[\text{moles/liter} \right], \tag{A.4}$$

where

T is the time of light exposure [s].

The probability that an activated drug (D^*) will transfer its excited state energy to oxygen to yield an oxidative radical (R^*) is specified by the quantum yield (Φ), which depends on the oxygen concentration in the tissue. The total amount of R^* produced is:

$$R^* = \phi D^* \quad \left[\text{moles/liter} \right]. \tag{A.5}$$

A fraction (f) of R^* succeeds in oxidatively damaging critical sites in the cell which contributes to cell death. The remaining fraction ($1-f$) attack relatively inert or noncritical sites. The accumulation (A) of critical oxidative damage is:

$$A = f \Phi \varepsilon \phi DT \frac{\lambda}{hc} \frac{1000}{6 \times 10^{23}} \quad \left[\text{moles/liter} \right]. \tag{A.6}$$

If the accumulated damage exceeds a threshold, $A > A_{th}$, then cell death occurs.

$$\textit{if} \quad A > A_{th}, \quad \text{then cell death.} \tag{A.7}$$

Oxygen

Oxygen is one of the three key ingredients of PDT (drug, light, oxygen). To simplify our mathematical treatment, we have lumped the effects of oxygen concentration into the quantum yield, which essentially assumes a constant oxygen availability. However, changes in blood perfusion during PDT can occur which cause O_2 to become a variable. Therefore, the dosimetry of oxygen during PDT should be considered when designing a reliable protocol. Spectroscopic monitoring of the oxygen tension of hemoglobin in a tissue is a convenient means of detecting changes in tissue perfusion, which is related to oxygen availability. A few laboratories (Foster et al. 1991; Tromberg et al. 1990) have addressed the dosimetry of oxygen concentration during PDT, and there is a recognized need for more such work.

Practical Dosimetry for the Clinic

Currently, the few laboratories concerned with rigorous PDT dosimetry routinely document the light reaching a tissue site (L), the amount of photosensitizing drug that accumulates in that tissue site (D), and the light exposure time (T), then calculate the total amount of drug activated during the light exposure period. This factor is quantifiable and therefore a practical dosimetric parameter that has been called the "photodynamic dose" by Patterson, Wilson, and Graff (1990). We have used the symbol D^* and the units of [moles/liter] to describe the photodynamic dose. Patterson and colleagues have described it as the number of photons absorbed by photosensitizing drug per gram of tissue [ph/g]:

$$\text{"photodynamic dose"} = D^* = \varepsilon D \phi T \frac{\lambda}{hc\rho} \quad [\text{ph/g}] , \tag{A.8}$$

where

ρ is the density of tissue [g/cm^3].

The "photodynamic dose" (D^*) does not consider the quantum yield (Φ) of oxidative radicals, the effect of oxygen on Φ, or the fraction (f) of radicals that oxidize critical sites. However, photodynamic dose is the dosimetric parameter most commonly documented. There is logic in this choice since light (L), drug (D), and exposure time (T) are parameters under experimental or clinical

control. Experimental determination of the margins of necrosis induced by a well-defined D^* can specify the threshold dose (D^*_{th}). The criteria for necrosis is then:

$$\text{if} \quad D^* > D^*_{th}, \quad \text{then cell death}. \tag{A.9}$$

For example, a typical D^*_{th} for some drugs is about 10^{19} [ph/g], which equals a 17 mM concentration of activated drug.

Treatment Zone

For the sake of illustration, consider a treatment using topical irradiation of a tissue surface with a broad beam of light a couple centimeters in diameter. The light penetration into the tissue can be described by the one-dimensional expression:

$$\phi = E\, k_s \exp\left(-z/\delta\right), \tag{A.10}$$

where

E = irradiance at tissue surface [W/cm^2],

ks = the backscattering factor which accounts for how reflected light from the tissue augments delivered light [dimensionless],

z = depth into the tissue [cm]

δ = the optical penetration depth [cm], the pathlength which causes the concentration of light to drop to 1/e or 37% of its initial concentration.

Also, assume that the depth of necrosis from such a topical PDT treatment is located at $z_{necrosis}$, which corresponds to the depth at which the threshold accumulation of oxidative damage, A_{th}, occurs. Then combining equation (A.9) and (A.10) and inserting $z_{necrosis}$ and A_{th} yields:

$$A_{th} = f\Phi\varepsilon DT\,\frac{\lambda}{hc}\,\frac{1000}{6\times10^{23}}\,E\,k_s \exp\left(-z_{necrosis}/\delta\right), \quad \left[\text{moles/liter}\right]. \tag{A.11}$$

Finally, rearrange equation (A.11) to solve for $z_{necrosis}$:

$$z_{necrosis} = \delta \ln\left(\frac{f\Phi\varepsilon\phi DT\,E\,k_s}{A_{th}}\,\frac{\lambda}{hc}\,\frac{1000}{6\times10^{23}}\right), \quad \left[\text{cm}\right]. \tag{A.12}$$

Equation (A.12) shows how the depth of necrosis depends on all the various parameters that affect PDT. Notice that $z_{necrosis}$ is linearly related to the optical penetration depth but logarithmically related to all other parameters. To double $z_{necrosis}$, one need only double δ but must alter any other factor 7.4-fold.

Again consider the practical dosimetry based on D^*, the photodynamic dose. If the irradiance at the tissue surface yields a $D^*_{surface}$ at the surface, then the depth of necrosis can be expressed:

$$z_{necrosis} = \delta \ln\left(\frac{D^*_{surface}}{D^*_{th}}\right), \quad [\text{cm}], \tag{A.13}$$

where

$$D^*_{surface} = \varepsilon DTEk_s \frac{\lambda}{hc}\frac{1}{\rho}$$

For example [adapted from Jacques (1992)], consider the PDT dosimetry using a generic photosensitizer (PS) to illustrate how to estimate the zone of treatment:

Photons

Wavelength	λ	630 nm = 630×10^{-7} cm
Irradiance	E	0.2 W/cm^2 = 0.2 J/(cm^2 s)
Exposure time	T	20 min = 600 s
Optical penetration depth	δ	0.51 cm
Optical backscatter factor	k_s	4.4 [dimensionless]
Conversion constant	λ/hc	0.2×10^{18} photons/J

Photosensitive Drug

Administered drug dose		5 mg/kg body weight = 5 μg/g.tissue
Molecular weight of drug	MW	600 g/mole
Tissue density	ρ	1 g.tissue/cm^3
Tissue concentration of drug	D	3 μg/g.tissue
= $(3\times10^{-6}$ g/g.tissue)(1 mole/600 g)(1 g.tissue/cm^3)(1000 cm^3/liter)		
= 5×10^{-6} moles/liter		
Extinction coefficient of drug	e	104 (cm^{-1})/(mole/liter)
Quantum efficiency of activating radicals	Φ	0.1 [dimensionless]

Photodynamic dose at surface	$D^*_{surface}$	8.4×1019 ph/g = 143 mmoles/liter

Tissue Treatment Zone

Threshold toxic product	D^*_{th}	1019 ph/g = 17 mmoles/liter
Zone of treatment	$z_{necrosis}$	1.1 cm

Therefore, the treatment zone, $z_{necrosis}$, is a depth of 11 mm for the above generic example of PDT using one-dimensional topical light delivery. To double $z_{necrosis}$, one need only double δ, but one must alter any other factor 7.4-fold.

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