Dosimetry in Pleural Photodynamic Therapy

Presented by Timothy C. Zhu, PhD, *University of Pennsylvania, Philadelphia, Pennsylvania*

Abstract

Photodynamic therapy (PDT) centers on the photochemical interaction of 3 principal components: light, photosensitizer, and oxygen. Over the past 25 years, much has been learned about the basic biophysical mechanisms of PDT, and in the future, a clearer understanding of the physics of PDT will make it possible to translate this science into improved clinical treatments. This article explores the role of explicit dosimetry in PDT and the need for individualized determination of dosimetric parameters based on the heterogeneity of optical properties and photosensitizer drug concentration. In addition, the use of a navigation system to help deliver uniform light for pleural PDT is briefly discussed. (*JNCCN* 2012;10[Suppl 2]:S60–S64)

Explicit Dosimetry: Heterogeneity in Tissue Optical Properties

Explicit dosimetry refers to the measurement of quantities related to the prediction of singlet oxygen dose, which is presumed to be predictive of tissue damage, based on measurable quantities that contribute to the photodynamic effect.[1] The principal quantities are generally the distributions of light, photosensitizer, and oxygen.[1] "We want to see how we can use light, drug, and oxygenation all together to better predict outcomes in different settings," revealed Dr. Zhu.

In current clinical practice, according to Dr. Zhu, the quantity most straightforward to measure is the light dose.[1] The absorption and fluorescence peaks of the photosensitizer HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) are shown by Kim et al.[2] They showed that the coencapsulating nanoparticles are actively taken up by tumor cells in vitro and that the excitation efficiency of HPPH is preserved in the intracellular environment.[2] "We are currently using HPPH for pleural PDT," reported Dr. Zhu.

"The absorption spectrum is one of the things we can use to determine concentration," he continued. Absorption is the attenuation of light in tissue, and the absorption spectrum can be used to determine the optical properties of underlying tissue, photosensitizer drug concentration, and oxygenation in tissue. "The apparatus commonly used in the clinic uses a linear optical probe, and the device has a white light source that you can shoot into the tissue," explained Dr. Zhu. "You will get signals at different distances from the light source, and these different signals can fit into a model, which will allow us to determine the penetration of light."

The penetration depth varies greatly among different organs (Table 1). For instance, the light penetrates more deeply in skin tissue than in liver tissue. "There is a lot of variation in the penetration depths," confirmed Dr. Zhu. "We see it not only in different tissue types and different patients but also in the same type of tissues and in the same patient."

Moreover, the absorption spectra can be used to determine oxygenation in PDT dosimetry. "One can determine the oxygenation by using the spectral shape difference between the oxyhemoglobin and deoxyhemoglobin," revealed Dr. Zhu. Currently, between 500 and 800 nm is the range widely used in this field, according to Dr. Zhu. "Then you can also determine the oxygen saturation, total hemoglobin concentration, and drug concentration because they have different spectra."

In a phase II clinical trial, Wang et al[3] extracted tissue optical and physiologic properties from 12 patients using a diffuse reflectance instrument and algorithms

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Table 1 Light Penetration Depth in Different Organs at 730 nm

Organ	$1/\mu_{eff}$ (mm)
Skin	5.6
Large bowel	4.9
Perineum	2.9
Kidneys	1.3
Liver	1.0

based on the diffusion equation. In their analysis of absorption data, they found that tumor blood oxygen saturation was significantly lower than oxygenation in normal intraperitoneal tissues in the same patients.[3] "There is a large variation in oxygen saturation between the tissue type [such as large bowel, small bowel, or peritoneum] and also in drug concentration," reported Dr. Zhu. "So even though patients are getting the same amount of drug, there may be a variation in uptake between patients and within the same patients," he clarified.

Variations in tissue optical properties were also shown by Dr. Zhu et al[4] in a study of cancerous human prostate during motexafin lutetium–mediated PDT. Based on the findings of their integrated system to determine these quantities before and after PDT treatment using motorized probes, they noted significant interprostatic and intraprostatic variations in the tissue optical properties and motexafin lutetium drug distribution. "You can also do fluorescence studies to determine the drug concentration," he emphasized.

In turning to the role of light in PDT, "The light fluence rate is the light that is getting into an infinitely small sphere from all different directions." To measure the incident irradiance at the tissue surface in intraoperative PDT, flat photodiode detectors were used.[1] However, isotropic detectors, which are used at Dr. Zhu's university, are a better option.

Dr. Zhu briefly reviewed the importance of real-time light dosimetry. "A great deal of heterogeneity in light dose to the superficial tissues is observed, not only in terms of light distribution itself but also in tissue backscattering," he explained. "The variation in light dose from patient to patient is due to heterogeneity in the tissue optical properties. The amount of light that is refracted out is dependent on the tissue optical properties."

Furthermore, the light dose delivered to the surface of the pleura using a flat photodiode versus an isotropic detector has been compared. Flat photodiodes do not accurately measure the fluence rate in the tissue itself because they neglect to consider the contribution of backscattered light.[1] Detectors based on optical fibers may overcome this problem through collecting light isotropically.[1]

Pleural PDT and Light Dosimetry

Dr. Zhu shared an update on a phase II trial of pleural PDT and surgery for treating patients with non–small cell lung cancer (NSCLC) with pleural tumor spread at his institution.[5] Of the 22 patients enrolled in the study, the median survival was 21.7 months, compared with historic median survival rates of between 6 and 9 months for patients with NSCLC and pleural tumor spread.[5] In this study, real-time dosimetry was used to measure the delivered light dose, making it a critical component for ensuring the safety of intraoperative PDT, assessed Dr. Zhu.

Dr. Zhu also illustrated the use of HPPH-mediated pleural PDT in a phase I study. The pleural PDT protocol includes a diagnosis of mesothelioma or pleural effusion, the administration of HPPH 24 to 48 hours before irradiation, a red light source of 15 to 60 J/cm^2 (at 665 nm), and delivery of light through continuously moving the point source in the thoracic cavity.

With pleural PDT, isotropic detectors are placed in the thoracic cavity (Figure 1). "Seven detectors are what we are using, and the goal is to have these 7 locations getting the same light source," explained Dr. Zhu. The 7 locations are the apex, the posterior mediastinum, the posterior chest wall, the posterior diaphragmatic surface, the anterior diaphragmatic surface, the anterior chest wall, and the pericardium. Surgeons experienced in pleural PDT ensure that the light is uniform between the interstitial spaces, he added. In addition, Dr. Zhu and colleagues at the University of Pennsylvania have correlated the treatment time versus the cavity surface treatment area and volume for the 12 patients for whom they have used pleural PDT, based on the use of pretreatment CT scans.

Navigation System: Taking Into Account Scattering Light

To improve the light dosimetry, Dr. Zhu and colleagues attempted to determine the light not only at the 7 detector points but also in between these points.

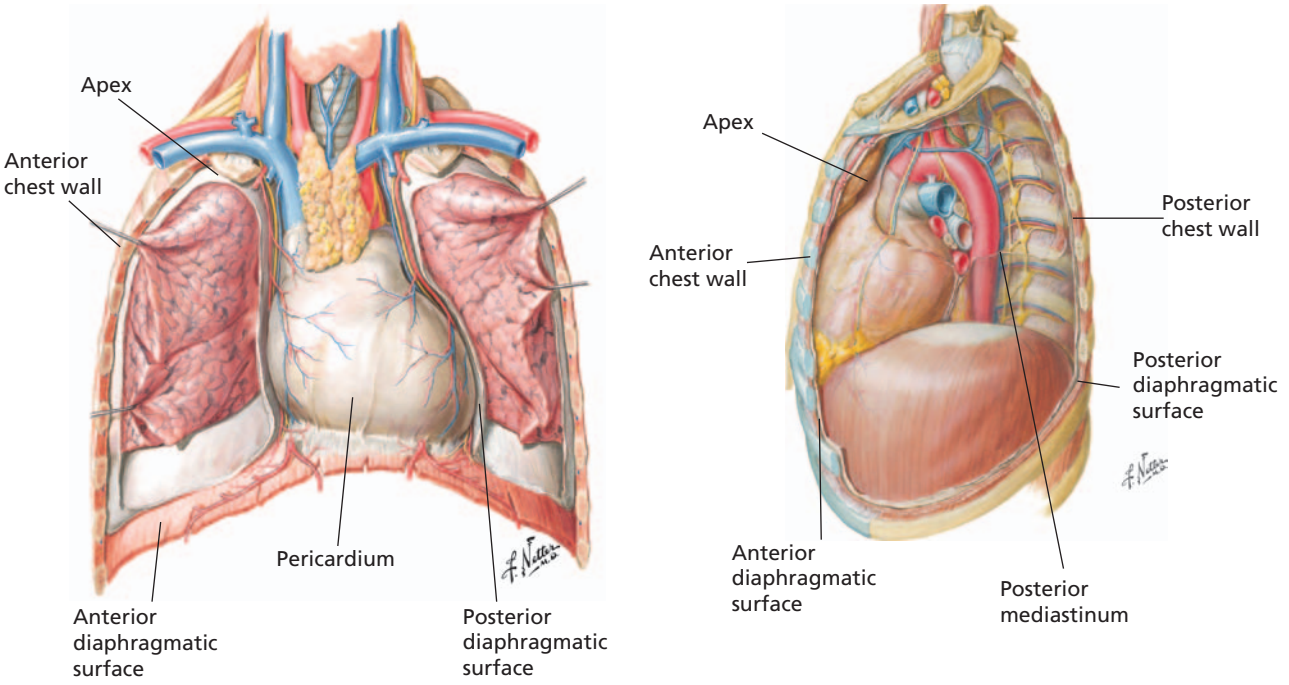

Figure 1 Isotropic detectors are placed in the thoracic cavity in 7 locations. Images used with permission from Elsevier. All rights reserved.

The placement of custom-made refractive markers on this device made it possible to track the motion of the point source. "So we will know exactly in real time where these point sources are," stated Dr. Zhu.

Based on an algorithm for calculating light fluence rates, Dr. Zhu and colleagues were able to compare their calculation with the measurement (Figure 2). "The calculation is typically less than the measurement, which is not surprising because we didn't account for scatter light, and, in fact, there is some scatter light," he clarified. Dr. Zhu then illustrated that using a new, more accurate methodology that takes into account scattering light allows one to obtain agreement in most cases (Figure 3). "With navigation guidance, you can improve the results further," he concluded. In addition, through using the point source tracking results, the entire light fluence on the entire pleural cavity can be calculated.

Singlet Oxygen Model for PDT Dosimetry

How do we account for the rate of PDT oxygen consumption, asked Dr. Zhu. In answering his own question, he turned to a PDT dosimetry model.[6] This macroscopic singlet oxygen model incorporates a light diffusion equation and a set of PDT kinetics equation.[6] The sensitizer plus light plus oxygen leads to singlet oxygen, the major cytotoxic agent responsible for cell killing for PDT.[6] "In the end, we want to use this model to capture the oxygen consumption during a PDT process," he explained. To do so, it is necessary to determine several photophysical parameters, photosensitizer retention, and tissue optical properties, which contribute to enhanced efficacy of PDT.[7,8]

To determine these parameters, Dr. Zhu and colleagues developed an in vivo mouse model. "The drug concentration used here is actually comparable to that used in humans," he added. "You will see necrosis, and we correlate that to the light fluence distribution. And we are using the isotropic detector to measure the light fluence and drug concentrations within this particular model. We were quite successful with these extensive experiments of various light fluences."

Conclusions

Explicit PDT dosimetry includes determining underlying tissue optical properties, photosensitizer drug

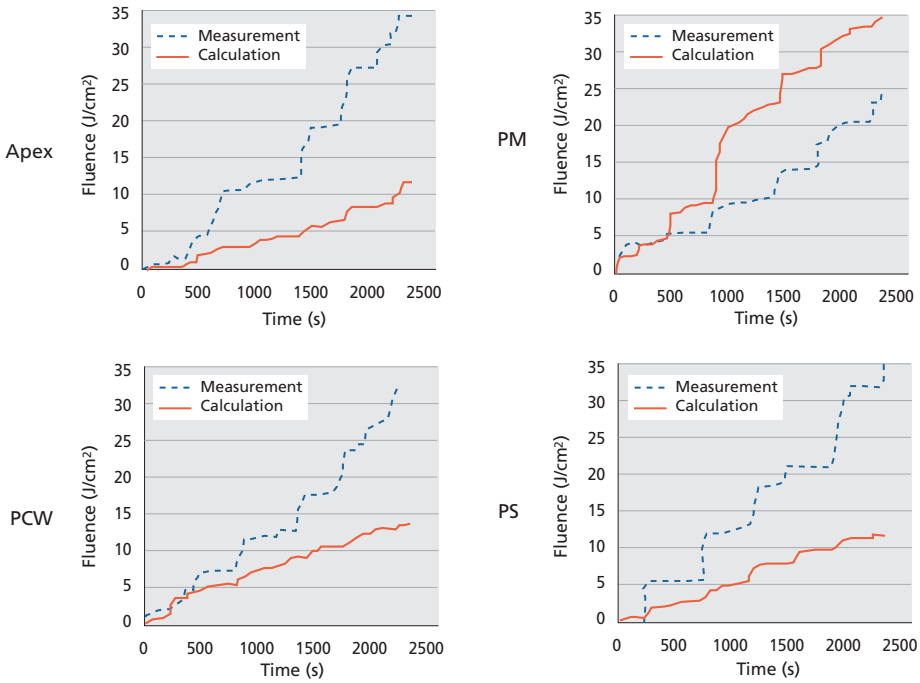

Figure 2 Light fluence comparison between the calculation and the measurement for 4 of the 7 detector locations: the apex, the posterior mediastinum (PM), the posterior chest wall (PCW), and the posterior diaphragmatic surface (PS).

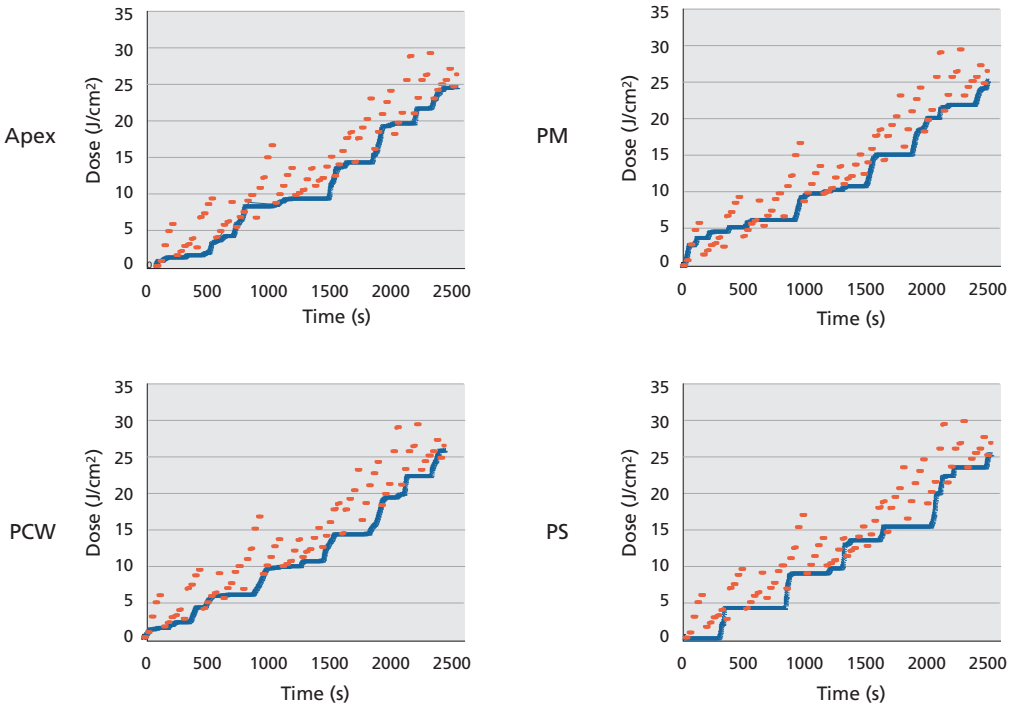

Figure 3 Comparison after corrections of the light fluence rate between the calculation and the measurement for the same 4 detectors in Figure 2: the apex, the posterior mediastinum (PM), the posterior chest wall (PCW), and the posterior diaphragmatic surface (PS).

concentration, and oxygenation. Tissue optics plays a dominant role in specifying the treatment zone during PDT. In vivo measurements strongly suggest that heterogeneity exists in optical properties and photosensitizer drug concentration, thus requiring individualized determination of these dosimetric parameters. A navigation system or other advanced technique may help ensure the delivery of uniform light for pleural PDT. A macroscopic singlet oxygen model can be used to better correlate the efficacy of PDT with treatment conditions, thus improving outcomes.

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