PHOTODYNAMIC THERAPY OF TUMORS:

DEFINITION OF PDT DOSE AND RESPONSE

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I. INTRODUCTION

The PDT dose at any point in tissue can be generally defined as the integral of the Photofrin II concentration over the time integrated space irradiance at that point. We know the dependence of Photofrin II concentration (i.e. photobleaching) as a function of the incident Joules/cm² for a thin superficial layer of tissue. If the space irradiance is also available as a function of the incident light for this geometry we can express the photobleaching of the Photofrin II as a function of the time integrated space irradiance in this layer (we assume that the space irradiance is constant in this thin layer). At this point knowledge of the space irradiance as a function of the incident flux for other simple geometries allows us to determine the PDT dose within the tissue for the clinically interesting cases of an implanted cylindrical source, a water filled bladder with a spherically isotropic source at the center, an implanted spherical source and the case of a uniform surface illumination.

Using the end point of depth of tissue necrosis and available clinical data for the case of surface illumination of skin¹, we can calculate the minimum photodynamic dose required for tissue necrosis using the generalized definition of dose. This value can then be used to predict the necrotic depth obtained in the other simple geometries. The available clinical data is in good agreement with these predictions.

Determination of the dependence of Photofrin II concentration on the time integrated space irradiance in tissue allows the definition of photodynamic dose to be formulated as an integral of sensitizer concentration over the time integrated space irradiance at each point in tissue. This integral, together with a measurement of the depth of necrosis produced by the clinically measurable sensitizer and light doses, and the tissue optical properties allows the calculation of the expected necrotic depth for any similar tissue. These predictive calculations are carried out for various dosimetric conditions and a variety of clinically interesting sources e.g. long cylinders or spherically symmetric sources imbedded in the tissue, uniform surface illumination over a wide field or a spherical source at the center of a water filled bladder. The results are presented in graphical form and are based on published clinical data.

¹ Laser Systems for Photobiology and Photomedicine
II. GENERALIZED PHOTODYNAMIC DOSE

The dose integral, $D$, has been defined by:

$$D = \int_{0}^{J} C(J) \, dJ$$  \hspace{1cm} (1)

$C(J)$ is the concentration of Photofrin II in a thin slab of tissue. From measurements of extractable Photofrin II as a function of $J$, the incident $J/cm^2$, we know that:

$$C(J) = C_0 \exp(-\beta J)$$  \hspace{1cm} (2)

where $C_0$ is the initial Photofrin II concentration and $\beta = 0.36 \, J/cm^2$ is the photobleaching rate constant: the photobleaching rate was determined in human tumors by measurement of the decrease in tissue fluorescence during treatment. The loss of fluorescence correlates well with the loss of extractable drug in mice.

Fortunately the determination of space irradiance within tissue as a function of the incident flux is a subject which has received both theoretical and experimental study. We will use the results of Reference 4 for all but the case of the water filled bladder where the results of Reference 5 will be employed.

Photodynamic therapy is mainly concerned with the use of 630 nm wavelength light where scattering is the dominant interaction with tissue. Space irradiance (the total light flux through an infinitesimal surface at a point in tissue) is best described by the results of diffusion theory which can be applied to light which is scattered multiply before absorption. As this scattering initially increases the space irradiance at the tissue surface the determination of space irradiance within the tissue is not a trivial problem because the clinically measurable quantity is the incident flux. The computer modeling techniques used to study the scattering of neutrons in the design of nuclear reactors have been applied in Reference 4 to produce equations for the space irradiance for some clinically interesting source geometries.

The result for a planar surface illuminated over a large area with a uniform dose $J_o \, (J/cm^2)$ is

$$\phi_t = \frac{4J_o \exp(-\alpha z)}{1 + \xi \alpha}$$  \hspace{1cm} (3)

where $\xi$ is the diffusion coefficient, $t$ is time in sec, $\phi$ is space irradiance in W/cm$^2$ and $\alpha$ is the tissue attenuation coefficient. Equation (3) is correct for a diffuse source. In PDT we are measuring the flux from a collimated source. However in all of the cases treated here the light passes through the skin which acts to provide significant diffusion. Thus we will use these results with the understanding that we assume the light becomes diffuse with negligible loss in the first 200$\mu$m of the skin surface. Thus this description of the space irradiance applies from just below the skin surface (the plane of $z = 0$). Substituting $\alpha = 3.3 \, cm^{-1}$, and $\xi = 0.07 \, cm$ in equation (3) gives

$$\phi_t = 2.7 \, J_o \exp(-\alpha z)$$  \hspace{1cm} (4)

Writing equation (2) in terms of space irradiance for $z = 0$, gives

$$\beta J_o = \beta^* \phi_t$$  \hspace{1cm} (5)