THOUSAND WORDS ABOUT...

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A thousand words about the challenges of photodynamic therapy

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ABSTRACT

The outbreak of interest in photodynamic therapy (PDT) at the end of last century to treat cancer and other diseases was based on the promise of localised treatment, cheaper therapy and fast ablation of the treated organ. One of the most attractive features of PDT is that it can evade cancer's resistance to photosensitisers. PDT for cancer therapy depends on the absorption of a photosensitiser within the malignant tissue. The photosensitising drug is then activated by light (usually from a laser) and the active drug destroys the targeted tissue. However, one must consider that this is a complex mechanism involving many factors such as the diverse light and oxygen distribution in the treated organs, which has mitigated application of this technique in clinical practice. PDT is not a simple treatment that can be done by eyeballing; it requires precise planning that can be done with the help of complex computer programs. Computer simulation of PDT to optimise treatment depends heavily on intense calculations in all steps of the procedure, and desktop computers are only now sufficiently powerful to assist physicians during therapy in real-time. In this mini-review, the challenges of photodynamic therapy are described, and possible to solutions to overcome these are presented.

Keywords: photodynamic therapy, cancer, computer simulation.

The explosion of interest in photodynamic therapy (PDT) at the end of the last century to treat cancer and other diseases was based on the promise of localised treatment, cheaper therapy and fast ablation of the treated organ. Many authors reported successful application of PDT techniques *in vitro* [1–6], but *in vivo*, PDT has been investigated to treat different diseases mostly when light can be easily delivered [1, 7–9]. Currently PDT is used mainly in dermatology, and in the treatment of glioblastoma and mesothelioma, and some efficacy of this modality has been demonstrated [10]. One of the most attractive features of PDT is that it can evade cancer resistance to photosensitisers [10–13]. However, one must consider that this is a complex mechanism involving many factors such as the diverse light and oxygen distribution in the treated organs, which has mitigated application of this technique in clinical practice [14].

PDT for cancer depends on the absorption of a photosensitiser within the malignant tissue. The photosensitising drug is then activated by light (usually from a laser) and the active drug destroys the targeted tissue. There are four major components of photodynamic therapy: light, photosensitiser, oxygen, and the tissue characteristics of the treated organ.

Light

The light used for PDT is usually in the wavelength range of around 600–800 nm, and is called

the therapeutic window. Light in this range has the right energy level (>1.5 eV) to excite the photosensitiser, and is a wavelength that ensures sufficient penetration into the tissue [15]. Higher wavelengths offer better tissue penetration [16, 17], thus, some authors define a therapeutic window up to 1000 nm, however some light absorption by water in the range above 900 nm must be considered as it will limit tissue penetration to some extent [18].

Photosensitiser

Quinones and porphyrin derivatives which absorb light in the therapeutic window are most frequently used in photodynamic therapy [19]. The photosensitiser should preferentially accumulate in cancerous tissue (at least twice as much as in the surrounding tissue) [20]. Sometimes, to increase the concentration in the PDT target, the photosensitisers are conjugated with an antibody specific to the cancer cells to increase drug build-up [16]. Upon being irradiated with a low-power light and absorbing photons, the sensitised photosensitisers in the presence of oxygen produce several radicals and reactive oxygen species (ROS). Among them, singlet oxygen is the primary active specimen causing necrosis in the treated organ [19, 21].

Tissue characteristics

The two parameters of greatest importance in photodynamic therapy are the attenuation coefficient (absorption and scatter coefficient of light within tissue), and the critical fluence (minimum energy of light needed to kill cancerous tissue). Both depend on the concentration of the active drug within the tissue. The distribution of light energy fluence φ_l in J cm^{-2}, around a cylindrical fibre, placed in a highly scattering medium, such as cancer tissue, is based on the diffusion equation:

$$\varphi_l = \varphi_o \exp(-r\,\mu_{eff})$$

where: φ_o is the energy fluence at the light source, μ_{eff} is the effective attenuation coefficient in cm^{-1} that describes the absorbing and scattering properties of the tissue, and r is the distance from the delivery fibre in cm [17]. This equation is sufficient to calculate the extent of treatment, as can be seen on **Figure 1**.

Computer simulation

This represents the ideal situation. In reality, light distribution from light diffusers is not cylindrical and the tumour is not cylindrical in shape either. This requires the three-dimensional shape of the tumour or treated organ to be obtained. For example, in the case of prostate cancer, the preferred treatment is to ablate the entire organ [22]. In this case, a three-dimensional model can be constructed from two-dimensional ultrasound images, including the positions of inserted light sources, as can be seen in **Figure 2**. Moreover, having multi-sensor probes, the spatial distribution of the optical properties can be measured.

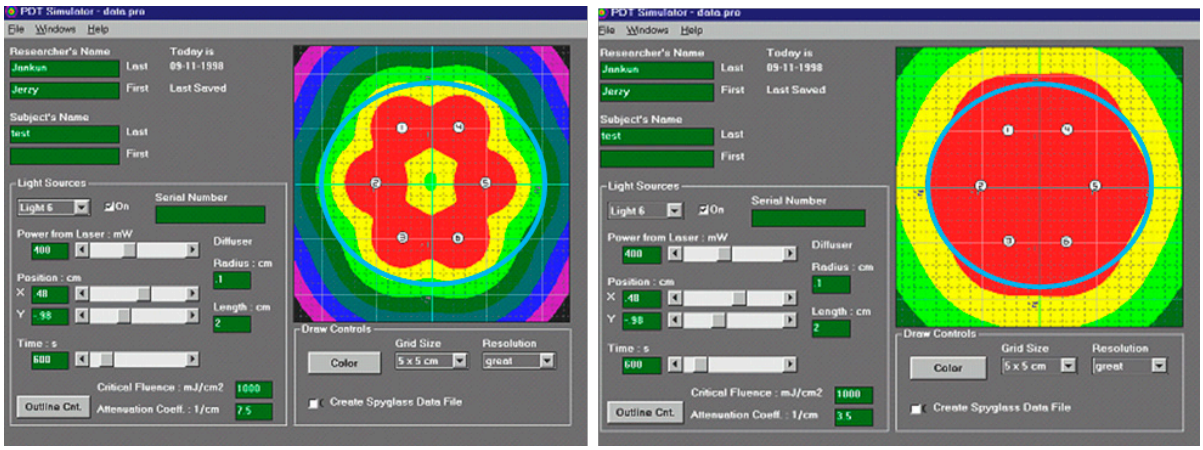

Figure 1. PDT computer simulation. Cross-section of imaginary cancerous tumour with (blue line) 6 light diffusers inserted into the tissue. The red areas represent the minimum light fluence required to effectively activate the drug and consequently ablate the tissue. Each successive colour band denotes isosurfaces of 10 times lower light fluency. *Left picture*: Not all cancerous tissue was ablated as the yellow colour inside the tumour indicates 10 times lower fluence than is needed for therapeutic ablation. *Right picture*: The red area filled the entire tumour cross-section when the critical fluence was smaller, or the time of treatment or light power was increased [20]

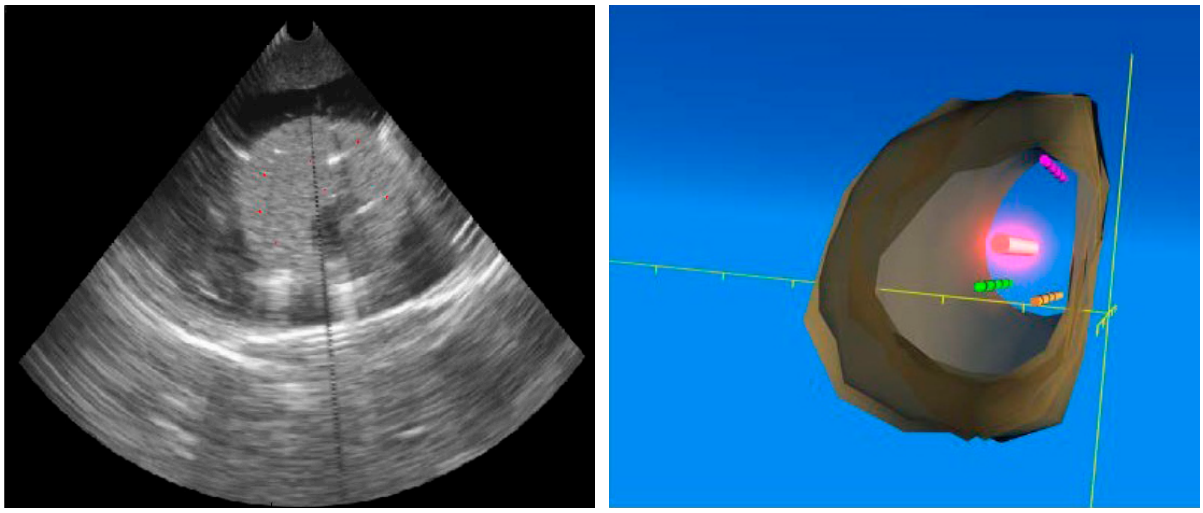

Figure 2. *Left picture*: Transverse ultrasound view of the prostate model showing the location of the laser diffuser and multi-sensor probes for fluence rate monitoring (white marks). *Right picture*: Model of the prostate based on transverse ultrasound images. For clarity, the base and apex of the model were "cut". The glowing red rod represents the light diffuser, and the three other rods represent multi-sensor probes for fluence rate monitoring

Uneven distribution of the photosensitiser within the treated organ is an additional complication of PDT. For example, we analysed the spatial distribution of a photosensitiser (tin etiopurpurin dichloride (SnET2) encapsulated in liposomes) in a canine prostate and found that its concentration varies between 1 and 2.5 μg of SnET2 per gram of tissue (**Figure 3**) [17].

The fluctuations of the photosensitiser within the treated organ can result in variation of the therapeutic PDT effects [21, 23]. Thus this parameter can be quantified by measuring the absorption of light between the light diffuser and segments of multi-sensor probes in a wavelength characteristic of the individual photosensitiser. The tissue's optical properties are influenced not only by the concentration of photosensitiser, but also by oxygenation of the blood, which can be measured in a similar way. Moreover, the amount of oxygen changes during photodynamic therapy, and the amount of photosensitiser changes as a result of consuming oxygen and the process of photobleaching. To account for these interactions, in addition to all of the parameters described above, a dynamic model of the photodynamic process is required to predict therapeutic tissue damage [15].

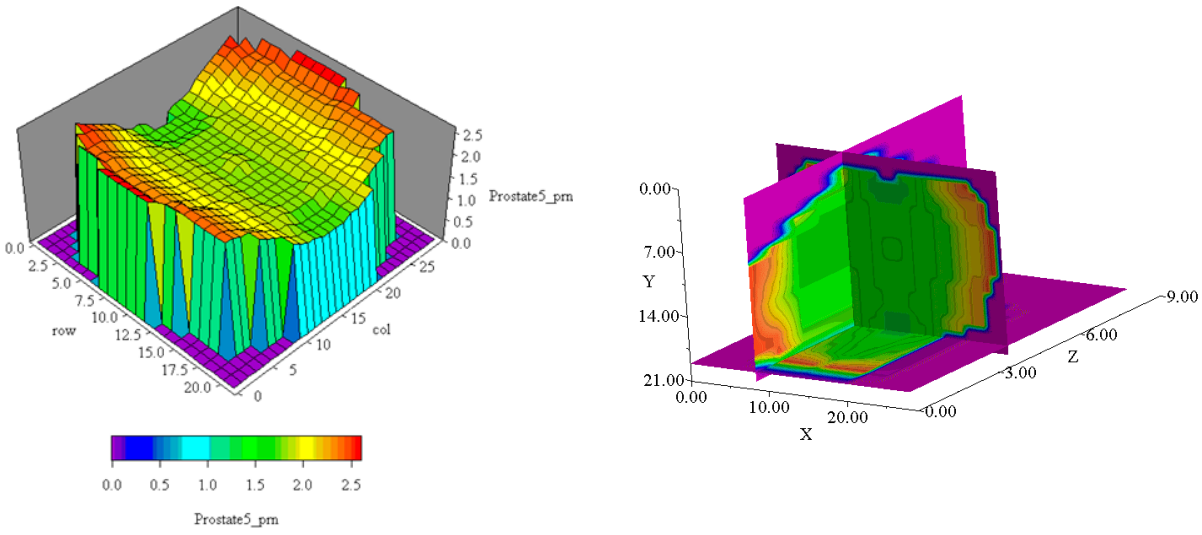

Figure 3. *Left picture*: Two-dimensional distribution of SnET2 within a canine prostate. *Right picture*: Three dimensional distribution of photosensitiser. Both images show the highest concentration of the drug in the peripheral regions of the gland [17]

Complete ablation will depend on precise placement of the light sources in the affected tissue, and the delivery of a therapeutic light dose. This will depend on a sequence of events: acquiring a three-dimensional tumour model, simulation to optimise the placement of the light sources, interstitial placement of the light sources, measurement of the above parameters of the treated organ, PDT computer simulation, evaluation of the treatment model and adjusting the parameters if needed, and finally executing PDT treatment based on all of these preparations.

PDT is not a simple treatment that can be done by eyeballing. It is a procedure that requires precise planning, which can be done with the help of complex computer programs [24–31]. Computer simulation of PDT to optimise treatment depends heavily on intense calculations in all steps of this procedure, and desktop computers are only now sufficiently powerful to assist physicians during therapy in real-time, to enable this therapy to treat a broad spectrum of malignancies.

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Conflict of interest statement
The authors declare no conflict of interest.

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