Predictive analysis of Photodynamic Therapy applied to esophagus cancer

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ABSTRACT

The use of optical techniques in medicine has revolutionized in many cases the medical praxis, providing new tools for practitioners or improving the existing ones in the fight against diseases. The application of this technology comprises mainly two branches, characterization and treatment of biological tissues. Photodynamic Therapy (PDT) provides a solution for malignant tissue destruction, by means of the inoculation of a photosensitizer and irradiation by an optical source. The key factor of the procedure is the localization of the damage to avoid collateral harmful effects. The volume of tissue destroyed depends on the type of photosensitizer inoculated, both on its reactive characteristics and its distribution inside the tissue, and also on the specific properties of the optical source, that is, the optical power, wavelength and exposition time. In this work, a model for PDT based on the one-dimensional diffusion equation, extensible to 3D, to estimate the optical distribution in tissue, and on photosensitizer parameters to take into account the photobleaching effect is proposed. The application to esophagus cancer allows the selection of the right optical source parameters, like irradiance, wavelength or exposition time, in order to predict the area of tissue destruction.

Keywords: Photodynamic Therapy, optical propagation, diffusion, photobleaching, esophagus cancer

1. INTRODUCTION

The use of optical techniques in medicine has allowed a great advance in the achievement of new and powerful tools in the fight against diseases. They also have provided improvements in the conventional methods. The application of this technology can be directed mainly to two principal objectives, depending on the needed medical target. On one hand, the interest can be concentrated on the diagnosis of pathological tissues. There are several optical techniques that deal with this aim, like Fluorescence Spectroscopy [1] or Optical Coherence Tomography [2]. On the other hand, the improvements of the application of optics to medicine can be applied to treatment of biological tissues. In this case, we can mention techniques like Thermotherapy [3], in which a slight temperature increase provokes an improvement in the pathological tissue, or Photodynamic Therapy (PDT) [4], which is the main purpose of this article.

Photodynamic Therapy is an optical technique whose objective is malignant tissue destruction. This tissue, usually cancerous, is destroyed by means of the inoculation of a photosensitizer. This substance is accumulated mainly in the region that is intended to be suppressed. The radiation exposition of the area makes the photosensitizer activate and it starts the destructive effect. Having this mechanism in mind, it is clearly seen that one of the main aspects of the application of this technique is the delimitation of the volume of tissue affected. The effort must be concentrated on the protection of adjacent tissues, to avoid these undesired collateral effects. The amount of tissue destroyed will depend on the substance inoculated in the tissue, on its reactive characteristics and its spatial distribution. It will also depend on the specific properties of the optical source used for irradiation, that is, optical irradiation, wavelength and exposition time.

In this work, the destructive effect of Photodynamic Therapy is analyzed and modelled, as a function of the optical source parameters and the photosensitizer characteristics. To achieve this objective, PDT is described first from the point of view of medical praxis, something necessary to start the modelling process. The construction of the model requires an optical propagation method in biological tissues. In this case, the diffusion approach of optical radiation is employed [1]. The fact that the optical beam could be considered spatially narrow or not is also taken into account. Optical energy

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deposition inside the tissue affects the photosensitizer properties, in such a way that its absorption varies due to the degradation provoked by the incident radiation. This effect must be also included in the model. All these considerations are used to construct a PDT model that estimates necrosis depth in tissue. The further adjustment of the parameters could lead to more precise destruction localization in the tissue under treatment. The model developed is applied to the specific case of esophagus cancer. The potentiality of the model and its predictive characteristics of the PDT treatment are shown by means of this application.

2. PHOTODYNAMIC THERAPY

As it was stated in the introduction, Photodynamic Therapy consists on the administration of a photosensitizer that is located and remains longer in malignant cells rather than in healthy ones. After this substance disappears almost completely from healthy cells, it is excited by optical irradiation at an appropriate wavelength, depending on the specific photosensitizer absorption response [4]. The amount of photosensitizer inoculated is not dangerous by itself, but when optically excited it encourages photochemical and photobiological processes that lead to a lethal effect in tumoral tissues.

The basic operational procedure of the photosensitizer action goes as follows. When the photosensitizer is irradiated with an appropriate optical source, it is excited. As it goes back to the ground state, the decays activate the molecular oxygen to create reactive oxygen species (ROS). These species are greatly cytotoxic, and as a consequence they provoke an irreversible oxidation of the essential cellular structures. In other words, the PDT is based on the use of a chromophore that catalyzes the reaction known as photosensitized oxidation. Most of the photosensitizers belong to organic dyes and their electronic states are characterized by singlets (with a total spin electron moment, s=0) and triplets (s=1).

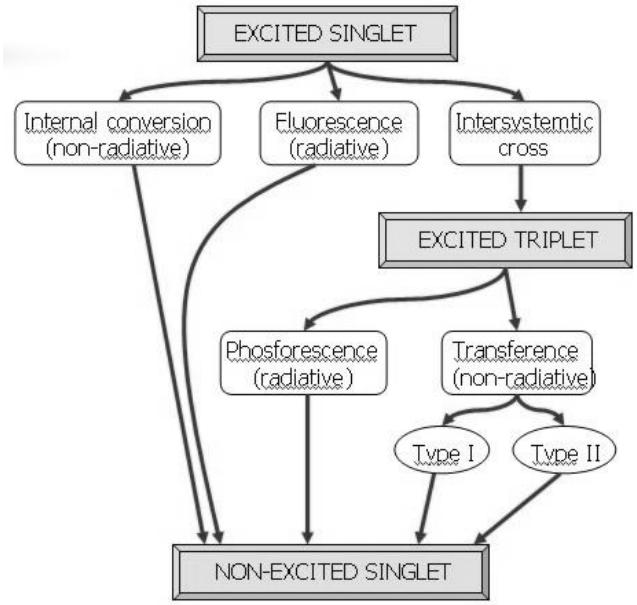

Fig. 1. Electronic transitions related with the photosensitizer that allow PDT treatment.

Regarding the interesting electronic transitions for PDT, whose scheme can be observed in Fig. 1, two different reaction mechanisms for the nonradiative decay from the excited triplet state can be considered. They are known as Type I and Type II. During the former reactions, the triplet state interacts with a molecule other than oxygen by electrons or hydrogen transference. This process results in the liberation of free radicals, which could be neutral or ionized. These radicals react quickly with triplet oxygen, and as a consequence produce reactants that are harmful for the cells, like hydroperoxides, hydrogen peroxide or superoxide anions. Meanwhile, the photosensitizer goes back to its ground state. In reactions of Type II, the triple state of the photosensitizer interacts directly with the triplet molecular oxygen $^3O_2$. Its energy state is increased and the triplet configuration leads to an excited singlet configuration $^1O_2$ as the photosensitizer goes back to the ground state. This singlet oxygen is very reactive and it can interact with a lot of molecular cells. This

interaction creates very cytotoxic products. So, as the singlet oxygen in reactions Type II reaches a particular concentration, it provokes a cellular oxidation and, as a consequence, necrosis. Reactions of both types, I and II, occur usually simultaneously, and they compete to obtain the reactants. Oxygen is absolutely necessary for these photochemical reactions, and so cellular necrosis could not appear in anoxic conditions [5].

There is an effect that has a great influence on the amount of photosensitizer and, as a consequence, on its distribution in cells. This is called photobleaching, and most of the photosensitizers used in Photodynamic Therapy show this behavior. This fact makes the selectivity of the therapy increase. Photobleaching is a permanent photochemical degradation of the chromophore due to the action of the products formed during the photochemical reactions. Having this in mind, the contribution of the photobleaching effect to PDT efficiency, in the sense of selectivity, is clear. The reason is related with the photosensitizer reduction in healthy adjacent tissues. If this concentration is reduced until it goes below the photochemical reactions threshold, no cytotoxic products are generated and no damage is provoked. Of course photobleaching implies also that the photosensitizer in malignant tissues could be extincted. If this takes place, all the subsequent irradiation would be useless, because no destruction would appear in tissue.

Photosensitizers are very important in PDT as we showed in previous paragraphs. Research about them is currently active. Among the most relevant ones, Photofrin® should be mentioned. It is one of the oldest photosensitizers, but it is also widely used and recognized. It could be considered a first generation photosensitizer. For the second generation, we have for instance ALA-PpIX (Aminolevulinic Acid – Protoporphirin IX). It is appropriate for superficial tumors and in the treatment of small areas. Its characteristics are quite similar to Photofrin®, but its selectivity could be even 10 times greater. Foscan® is another photosensitizer, and it is the most active, due to the small amounts of product needed and the little light dose for an efficient treatment. Other relevant photosensitizers are Benzoporphyrin Derivative (BPD), N-Aspartyl Chlorin e6 (Npe6), Lutetium Texaphyrin (Lu-tex) or Tin Etiopurpurin, SnET2 (Purlytin) [4].

The optical sources used in Photodynamic Therapy are mainly fluorescent lamps, diodes or laser sources. Laser sources present important advantages, like their spatial precision, the possibility of adjusting the wavelength (if they are tunable), or even the access to internal organs by means of endoscopes. However, sometimes these advantages are not required and the final decision depends on a trade-off between the usually high cost of a laser and the specific treatment characteristics.

Although the main application of PDT is the destruction of cancerous tissue, it can also be employed in other medical procedures. For instance, PDT could also be used in the fields of dermatology, ophthalmology (Age-related Macular Degeneration), molecular biology or even esthetics [5].

The complexity of the biological mechanisms of PDT, and also the great amount of parameters that appear in the election of the photosensitizer and the optical source make PDT dosimetry a fundamental point in this kind of treatment. That is the reason why we propose a PDT model to try to predict the PDT destruction effect. Next section describes the basics of this model.

3. PHOTODYNAMIC THERAPY MODEL

One of the main problems of Photodynamic Therapy modeling is the fact that a lot of parameters must be taken into account. These parameters depend on many variables, and it is not possible to record all of them in a non-invasive way. The complexity of the reactions inside the human body makes this task almost impossible. Due to these constraints, the existence of a tool that allows the simulation of the PDT process could be useful in order to predict the consequences of the treatment. These results will depend on the specific tissue treated, the optical source used and the photosensitizer involved. The potential of the PDT treatment could be extended by means of this tool, because it would allow the appropriate election of all the parameters involved in the process to obtain the desired effect.

Photodynamic Therapy modeling requires the appropriate consideration of optical propagation in tissue. This is a basic step in order to predict where the energy will be deposited and, consequently, which effects will take place. There are several approaches to model light propagation in tissue [1]. As it is known, the fact that biological tissues are heterogeneous media makes this task even more complex, because analytical solutions are only available for simple geometries, like spheres or cylinders [6]. As a consequence, an abstraction consisting of substituting the real tissue with an ideal material in which spheres of another material are randomly located is usually assumed. With this model, the effects that are taken into account are reflection, absorption and scattering, and therefore the parameters that describe light propagation in tissue are the index of refraction n (dimensionless), the absorption coefficient $\mu_a\,(m^{-1})$ and the

scattering coefficient $\mu_s\,(m^{-1})$. In this kind of problems, the most difficult effect to model is scattering, because its appropriate study has to do with different approaches related with the ratio between light wavelength and particle size, in the so called geometric, Rayleigh and Mie analyses [7].

In the problem we are dealing with, we use the diffusion theory to model optical propagation in tissue. This theory describes precisely radiation transport in a medium that presents dominant scattering over absorption properties. This is the case in most biological tissues when working at the typical wavelengths of PDT [1]. In the diffusion model, tissues are characterized, from the point of view of optical propagation, by the following parameters: refraction index; reduced scattering coefficient $\mu_s^{'} = (1-g)\cdot\mu_s$, where g is the anisotropy of scattering; and the absorption coefficient $\mu_a^{'} = \mu_{a0} + \mu_{aPS}$, where μ_{a0} is the tissue absorption coefficient and μ_{aPS} is that of the photosensitizer. All these parameters allow the calculation of the total transport coefficient $\mu_t = \mu_a^{'} + \mu_s^{'}$, the effective coefficient $\mu_{eff}(z) = \sqrt{3\mu_a^{'}(z)\times\mu_t^{'}(z)}$ and the diffusion constant $D = \dfrac{1}{3\left(\mu_a^{'} + \mu_s^{'}\right)}$.

The diffusion model is expressed by a diffusion equation. In the problems related with PDT it can be usually assumed to have a semi-infinite medium, initially homogeneous, and irradiated by a spatially wide beam. The photosensitizer concentration under these assumptions depends strongly on the depth coordinate, and less on the radial direction. As the photosensitizer absorption coefficient and the diffusion constant follow also this tendency, the problem can be reasonably simplified to a one-dimensional geometry. The diffusion equation under all these conditions and with only depth dependence is expressed as:

$$D(z)\frac{\partial^2\phi(z)}{\partial z^2} - \mu_a(z)\phi(z) = -S(z) \qquad (1)$$

In this equation, D is the diffusion constant, $\phi(z)$ represents the irradiance in the tissue, and $S(z)$ takes into account the optical source power per unit volume. This equation provides the values of the optical irradiance inside the tissue when irradiated with a specific optical source. Considering that the effective coefficient and the total transport coefficient vary slowly as depth increases, in such a way that they could be treated as constants, and also taking into account the boundary condition $\Phi(\infty)=0$, a semi analytic solution could be implemented. Any case, pure numerical solutions are also available for this problem. A finite difference numerical method can be used to obtain a solution for the fluence rate [8].

Equation (1) provides a stationary solution for the optical distribution inside an irradiated tissue. It assumes that the optical properties of the biological tissue are constant, at least in the same layer. However, as we stated previously, our biological tissue is affected by a photosensitizer during PDT. This substance suffers from the photobleaching effect, and this must be taken into account because it changes the optical absorption of the sample. The total absorption coefficient used in the diffusion equation is composed by the contribution of the tissue and that of the photosensitizer, $\mu_a^{'} = \mu_{a0} + \mu_{aPS}$. In the range of typical irradiations of PDT the tissue absorption coefficient remains constant, but the photosensitizer absorption coefficient varies with irradiation time. This variation must be properly modeled. It depends on the photosensitizer itself, and one approach is to state that the photobleaching kinetics follows a first order function [9]:

$$\frac{d\mu_{aPS}(z,t)}{dt} = -\beta.\Phi(z,t).\mu_{aPS}(z,t) \qquad (2)$$

In this equation, β is the so-called photobleaching rate of the photosensitizer (m^2/J). This parameter shows the relationship between the absorption decay and the fluence rate at that point of the tissue. Using equations (1) and (2) it is possible to predict the fluence rate that irradiation provokes inside the biological tissue.

As PDT is a destructive therapy for malignant tissues, a criterion must be established to decide whether the combined irradiation plus photosensitizer was enough to destroy cells or not. A very interesting parameter that deals with this topic is the so-called photodynamic dose D. PDT is a process that needs oxygen to appear, as we stated before. A parameter called singlet oxygen quantum yield, γ_0, gives an idea of the amount of toxic products created by the

reactions. It can be considered constant during the PDT treatment. The fluence rate and the photosensitizer absorption must be also relevant parameters for the photodynamic dose D. Next equation shows how this dose is modeled:

$$\frac{dD}{dt} = \gamma_0 . \Phi(z,t) . \mu_{aPS}(z,t) \quad (3)$$

The photodynamic dose can be seen as a time accumulated oxygen rate, which depends of course on the fluence rate and photosensitizer absorption. In order to limit the damaged zone, a dose threshold, D_0, must be established for the particular tissue of the PDT treatment. Equations (1), (2) and (3) provide a complete model for PDT damage prediction.

When applying PDT treatment, it is also interesting to try to monitor de destruction process. One approach to deal with this objective is to measure the fluorescence of the tissue under PDT treatment. As we use a one-dimensional model, the theoretical fluorescence calculus depends on whether the spatial profile of the optical source is wide or narrow [9]. In the former case, the local fluorescence emission inside the tissue is calculated as a product of the local fluence rate, the photosensitizer absorption coefficient and the fluorescence quantum yield γ:

$$f(z) = \gamma . \Phi(z) . \mu_{aPS,x}(z) \quad (4)$$

The *x* subindex implies that the optical properties are referred to the excitation wavelength, rather than the treatment wavelength. The fluorescence that reaches the tissue surface can be calculated considering a uniform fluorescence layer along the entire surface. The total fluorescence would be:

$$F(0) = \gamma . \int_0^\infty E(0; z_s) . \Phi(z_s) . \mu_{aPS,x}(z_s) . dz_s \quad (5)$$

$E(0; z_s)$ is the probability that the fluorescence from an isotropic point source at a depth z_s reaches the surface.

If the optical source has a narrow spatial beam, then two subcases appear [9]. It could be the case that scattering dominates over absorption, that is, $\mu'_{s,x} >> \mu'_{a,x}$, or that absorption dominates scattering, $\mu'_{a,x} >> \mu'_{s,x}$. In the former case, the optical source can be substituted by a scattering point and, by means of Green functions, the total fluorescence emission would be:

$$F(\rho', 0) = \int_0^\infty \int_0^\infty \int_0^{2\pi} E(\rho', 0; \rho_s, z_s) . f(\rho_s, z_s) . \rho_s . d\theta . d\rho_s . dz_s \quad (6)$$

If the absorption dominates, then a line of fluorescence sources along the optical beam axis is assumed, and the total fluorescence is:

$$F(\rho', 0) = \gamma . \int_0^\infty \left(\mu_{aPS,x}(z_s) . e^{-\int_0^{z_s} \mu_{a,x}(z) . dz} . E(\rho', 0:0, z_s) \right) . dz_s \quad (7)$$

All these equations provide a model for the prediction of the damaged area when applying a PDT treatment on a biological tissue. Equations can be solved by several numerical procedures, essentially by finite difference methods.

Next section describes the application of this model to the specific case of esophagus cancer.

4. APPLICATION TO ESOPHAGUS CANCER

Esophagus cancer is a severe pathology that consists of the formation of malignant tumoral cells in esophagus tissues. It starts in the inner layer, and it grows to the outer part of the esophagus, through the different layers, as the cancer goes further. Among the principal conventional therapies to treat esophagus cancer are surgery, radiotherapy or chemotherapy. All these procedures present strong secondary effects, and in the case of surgery it is highly invasive, because it suppresses the affected part of the esophagus. The application of PDT to this kind of disease by means of an endoscope could be of great importance, as it constitutes a safer procedure for cancerous tissue elimination. Fig. 2 shows

a scheme of the different evolution stages of the esophagus cancer, including the affection of the general immune system when the pathology is greatly developed.

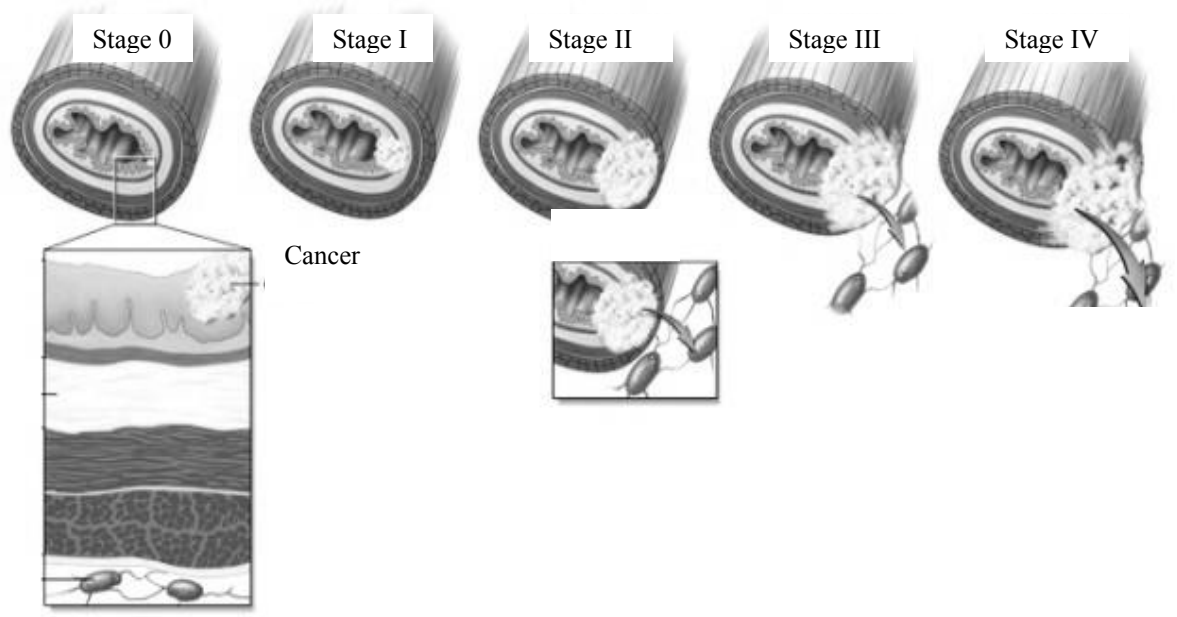

Fig. 2. Different stages of esophagus cancer. It starts in the inner layer of the esophagus and grows through the other layers until it reaches the immune system of the body [NC].

Here we try to apply the previously exposed model to this specific PDT application. The model is based on the optical parameters of the tissue, mainly scattering and absorption coefficients. These parameters, measured for a wavelength of 630 nm, appear in Table 1 [10], either for healthy esophagus or for cancerous esophagus tissue. The index of refraction of the esophagus is n=1.37.

Parameter	**Healthy esophagus**	**Cancerous esophagus**
Absorption coefficient (mm^{-1})	0.21	0.13
Scattering coefficient (mm^{-1})	12.56	9.35
Anisotropy of scattering	0.94	0.92

Table 1. Optical parameters of healthy and cancerous esophagus at 630 nm.

In order to apply the model, we consider a narrow spatial optical source coming from an endoscope inside the esophagus. The photosensitizer employed is Photofrin®, and this implies that the wavelength should be 630 nm. From Table 1 it is easily seen that scattering dominates over absorption. The initial absorption coefficient and the photobleaching rate are $\mu_{aPS} = 0.02$ mm^{-1} and $\beta = 0.05$ cm^2 / J [9].

The diffusion equation was solved via a numerical explicit finite difference method. The time step was chosen sufficiently low so as to make the method converge, and the execution time remain reasonably low. After every time step, the optical absorption of the photosensitizer was updated in order to take photobleaching into account. Different initial irradiances were considered, and the results were obtained as a function of the exposition time.

Fig. 3a shows the evolution of the fluence rate in depth as the time increases, when the source irradiance is 25 W/cm^2. Fig. 3b shows how the photosensitizer absorption changes under the same conditions.

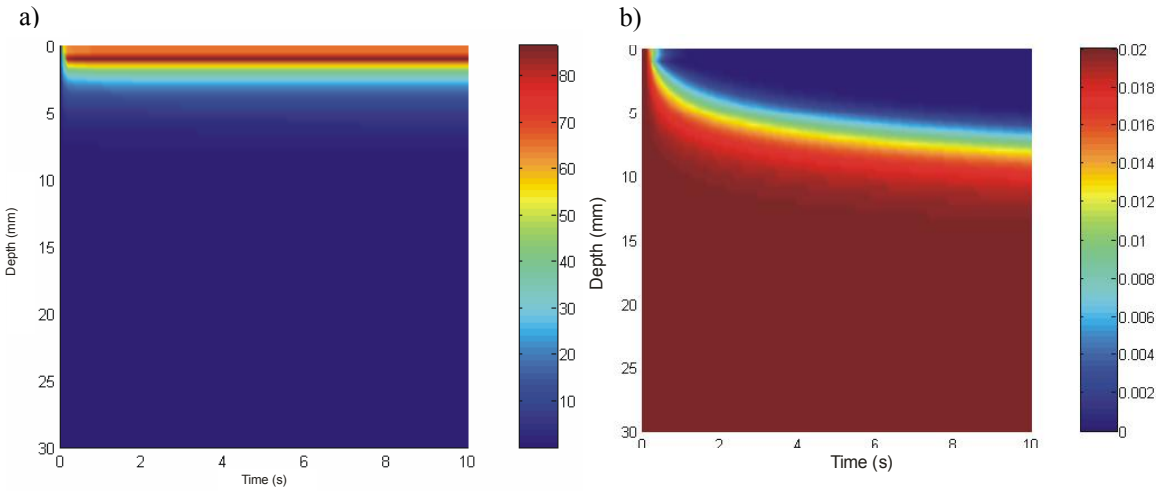

Fig. 3. Fluence rate (a) and photosensitizer absorption (b) as a function of tissue depth and exposition time, for an initial irradiance of 25 W/cm^2.

The model allows also the calculation of the amount of tissue destroyed, by means of the photodynamic dose. Fig. 4 shows different initial fluence rates and necrosis depths as a function of exposition time.

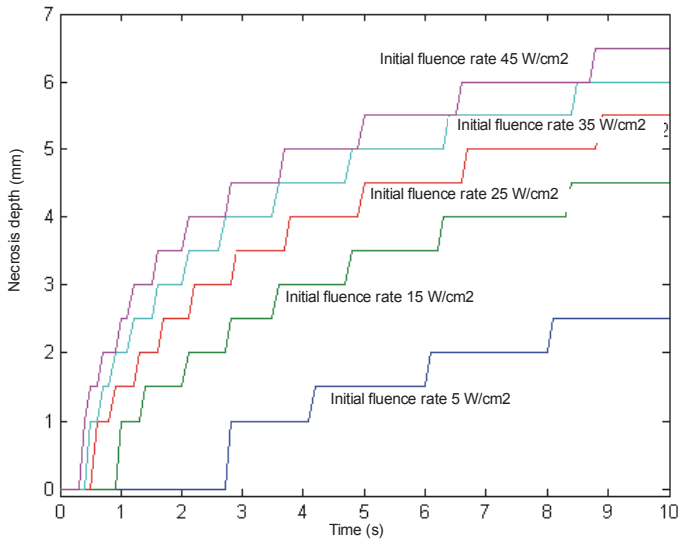

Fig. 4. Necrosis depth for different initial irradiances as a function of exposition time.

Fig. 3a shows how the irradiance is distributed inside the tissue, and penetrates more as exposition time increases. Fig. 3b shows the evolution of the photosensitizer absorption. As the total fluence increases with constant irradiation and exposition time, photobleaching appears and photosensitizer absorption diminishes. This effect takes place to a greater extent near the surface, where the irradiation is higher. Fig. 4 represents the fundamental aim of PDT prediction, because shows the depth extension of tissue necrosis. As expected, depth necrosis increases as exposition time is higher and as the initial fluence rate increases. In this way, these parameters can adjust the appropriate necrosis volume, depending on the severity of the tumor under treatment. Particularly, in esophagus cancer, 1 to 3 mm tumors are usually encountered. This means that it would be possible, according to the model, to use an irradiance of 5 W/cm^2 during tens of seconds, or even 15 W/cm^2 during only seconds. Of course other non-desired collateral effects like thermal damage must be also taken into account, because applying a very high irradiance during a very short time could lead to another type of laser-tissue interaction, like photoablation.

Any case, this tool allows the adjustment of the source parameters according to the tissue under treatment and the photosensitizer used, by predicting necrosis depth in the particular case of esophagus cancer.

5. CONCLUSIONS

Photodynamic Therapy (PDT) provides a useful tool for malignant tissue destruction, avoiding the non-desired secondary effects of more aggressive therapies like surgery or radiotherapy. A photosensitizer is inoculated in the tissue and optical irradiation activates the necrosis process. In order for the PDT treatment to be efficient, it is necessary to adjust the irradiance of the optical source, as long as the exposition time, depending on the particular tissue under treatment and the photosensitizer used.

In this work, we applied a predictive PDT model to esophagus cancer. Photofrin® was used as photosensitizer and an optical source with a 630 nm wavelength. The model uses a one-dimensional diffusion equation for optical propagation inside the tissue. The photobleaching effect, that is, the degradation of the photosensitizer with irradiation, is taken into account. A photodynamic dose is defined to predict tissue necrosis at each point in the tissue. The equations were solved via numerical finite difference methods, changing the total absorption in each time step. The results show the fluence rate inside the tissue, the degradation of the photosensitizer absorption and the different necrosis depths as a function of initial irradiance and exposition time. For instance, an irradiance of 5 W/cm^2 during tens of seconds, or even 15 W/cm^2 during only seconds can lead to 1 to 3 mm necrosis depths. Of course other non-desired collateral effects like thermal damage must be also taken into account, because applying a very high irradiance during a very short time could lead to another type of laser-tissue interaction, like photoablation. This information can be used in the achievement of an effective PDT endoscopic treatment of esophagus cancer, adapting the parameters to the extent and characteristics of the tumor.

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