Journal of Engineering Physics and Thermophysics, Vol. 72, No. 5, 1999

THERMOPHYSICAL EFFECTS IN PHOTODYNAMIC TUMOR THERAPY

V. N. Bidnenko and V. L. Sigal

UDC 616.33.002.44

A mathematical model of temperature modes in photodynamic therapy of brain tumors is suggested. Technological conditions for this therapy under which destruction of malignant cells along with photoprocesses are accompanied by hyperthermal and thermotherapeutic temperatures are determined. The realized possibilities allow one to achieve a higher degree of tumor destruction especially for low-perfusion tumors, with nearby healthy tissue being preserved.

Photodynamic therapy (PhDT) as a method for destroying tumor tissue is considered to be one of the most promising in clinical oncology. The biophysical mechanisms providing the clinical effect of this medical technology are insufficiently studied, thus making use of PhDT in medicine very uncertain. In practice, the conditions for implementing PhDT are very diverse and do not allow for the individual properties of a specific tumor. The majority of researchers consider that the destruction of tissue in PhDT is determined by the interaction of laser radiation with photosensitizers in the tumor. As a result of this physicochemical interaction, active forms of oxygen possessing a destructive action on the tumor cells appear as products of the reaction. These specific mechanisms are principal, though other mechanisms, such as hyperglycemia, activity of molecules of higher states of photosensitizers, etc., which facilitate the therapeutic effects of PhDT, are realized; the latter are less important [1, 2].

Temperature is also among the physical factors that cause cell damage. It is known that local hyperthermia – the establishment of a temperature of 42–43°C in a tumor – is considered an expedient physical method for affecting malignant growths [3]. Numerical experiments with cultures confirm that these hyperthermal temperatures destroy tumor cells. The development of thermal therapeutic methods in oncology facilitates the creation of new medical thermotherapeutic technologies which come down to the attainment of local temperatures of 70°C and higher.

By virtue of these effects, there exist a great number of publications offering a combination of PhDT and hyperthermia in which an intensification of the inactivation of abnormal cells has been observed [4, 5]. For clinical conditions, the order of use of the procedures for the greatest therapeutic effect is discussed in [6]. Since, however, PhDT uses laser-radiation energy, there arises the problem of determination and control of temperature modes in irradiated tisssue under this effect. This problem should be most adequately formulated for a two-layer model. This is explained by the fact that this model allows one to account for different optical and perfusion properties in two zones of tissue: the narrow surface zone destroyed by the PhDT process, which consists of the destroyed cells and blood flow system; and the remaining tissue.

For simplicity, we consider a one-dimensional two-layer semiinfinite medium which is irradiated from one side. These conditions determine the interstitial delivery of laser radiation directly to abnormal tissue. The first layer ($x \in [0; L]$, $i = 1$) has the optical characteristics of blood, which reflect its structureless character ("blood porridge"); convective heat transfer by blood flow is absent here, and this is essential for writing a corresponding biothermal equation. The second layer ($x \in [l; +\infty]$, $i = 2$) has ordinary optical and perfusion properties. Assuming the correctness of the use of the classical biothermal equation and the Bouguer–Lambert–Beer law, the corresponding system of equations takes the form:

Taras Shevchenko Kiev University, Kiev, Ukraine. Translated from Inzhenerno-Fizicheskii Zhurnal, Vol. 72, No. 5, pp. 946-950, September-October, 1999. Original article submitted October 20, 1998; revision submitted December 16, 1998.

1062-0125/99/7205-0915$22.00

$$\rho c \frac{\partial T_1}{\partial t} = \chi \frac{\partial^2 T_1}{\partial x^2} + I_0 \varepsilon_{ab} \exp(-\varepsilon_{tb} x);$$

$$\rho c \frac{\partial T_2}{\partial t} = \chi \frac{\partial^2 T_2}{\partial x^2} - c_b \rho_b \rho \omega (T_2 - T_0) + I_0 \varepsilon_{at} \exp(-\varepsilon_{tb} L) \exp(-\varepsilon_{tt}(x - L));$$

$$-\chi \frac{\partial T_1}{\partial x} = \alpha (T_1 - T_0)_{x=0}; \quad (T_2 - T_0)_{x=\infty} = 0; \tag{1}$$

$$(T_1 - T_0)_{t=0} = 0; \quad (T_2 - T_0)_{t=0} = 0;$$

$$(T_1 - T_2)_{x=L} = 0; \quad \left(\frac{\partial T_1}{\partial x} - \frac{\partial T_2}{\partial x}\right)_{x=L} = 0.$$

In (1) the possibility of cooling from inside the surface of the tip delivering laser radiation directly to tumor tissue by a flow of air or washing water (usually, distilled water) at temperature T_0 is taken into account.

In order to reveal the physical nature of the considered combination of processes of destruction of tumor tissue, we do not complicate system (1) by account for motion of the phase interface between the two layers. A further simplification can be realized if we restrict ourselves to estimations for stationary situations. Then, for the times of establishment of a stationary state in the first layer t_1 and in the second layer t_2 we obtain the following formulas by writing ordinary equations of heat balance for the tissue

$$t_1 \approx c\rho L/\alpha; \quad t_2 \approx 1/(\rho_b \omega). \tag{2}$$

This gives for the thermophysical constants of brain tissue $\chi = 0.5$ W/(m·°C), $c_b = c = 4$ kJ/(kg·°C), $\rho = \rho_b = 1040$ kg/m^3 and $t_1 = t_2 =$ min at $\alpha = 140$ W/(°C·m^2), $L = 2$ mm, $\omega = 1$ ml/(g·min).

We now estimate the velocity of variation of L. If $t_1 \approx t_2$, this limits the choice of values $L = 1-5$ mm. For these values, the times of irradiation in PhDT are about 1 h [7, 8]. Under these conditions, the rate of variation of these linear dimensions of abnormal tissue L can comprise $\approx$ (1/60–1/12) mm/h. Thus, use of stationary solutions of system of equations (1) is quite reasonable for practical situations. The spatial temperature distributions in each of the two layers in dimensionless quantities

$$\beta^2 = \frac{L^2 c_b \rho_b \rho \omega}{\chi}; \quad Q_b = \frac{I_0 L^2 \varepsilon_{ab}}{\chi T_0}; \quad Q_t = \frac{I_0 L^2 \varepsilon_{at}}{\chi T_0}; \quad \mathrm{Bi} = \frac{\alpha L}{\chi};$$

$$\Theta_i = \frac{T_i - T_0}{T_0}; \quad \xi = \frac{x}{L}; \quad \mu_b = \varepsilon_{tb} L; \quad \mu_t = \varepsilon_{tt} L \tag{3}$$

can be represented by the following analytical relations

$$\Theta_1 = -\frac{Q_b}{\mu_b^2} \exp(-\mu_b \xi) + A\xi + B;$$

$$\Theta_2 = D \exp(-\beta\xi) + \frac{Q_t}{\beta^2 - \mu_t^2} \exp(\mu_t - \mu_b) \exp(-\mu_t \xi); \tag{4}$$

$$B = \frac{1}{\mathrm{Bi} + \mathrm{Bi}\beta + \beta} \left[\frac{Q_b}{\mu_b}\left(1 + \frac{\mathrm{Bi}}{\mu_b}\right)(1 + \beta) + \left\{\frac{Q_b}{\mu_b^2}(\beta - \mu_b) + \frac{Q_t}{\beta + \mu_t}\right\} \exp(-\mu_b)\right];$$

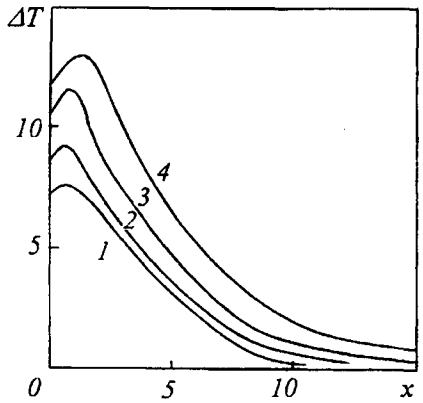


Fig. 1. Temperature increment in two-layered model of destruction of brain tissue in PhDT ($\varepsilon_{ab} = 0.62$ mm^{-1}, $\varepsilon_{tb} = 1.2$ mm^{-1}, $\varepsilon_{tt} = 1$ mm^{-1}, $\varepsilon_{at} = 0.5$ mm^{-1}, $I_0 = 500$ mW/cm^2, $\omega = 0.5$ ml/(g·min)): 1-4) calculated for values of L (mm) equal to 0 (a one-layered perfusion model), 1, 3, 5, respectively. ΔT, °C; x, mm.

$$A = \mathrm{Bi}\cdot B - \frac{Q_b}{\mu_b}\left(1 + \frac{\mathrm{Bi}}{\mu_b}\right);\quad D = \left\{A + B - \left(\frac{Q_b}{\mu_b^2} + \frac{Q_t}{\beta^2 - \mu_t^2}\right)\exp(\beta)\right\}.$$

Formulas (4) are valid at $\beta \neq \mu_t$. An analysis showed that, otherwise, at $\beta = \mu_t$ the stationary solution (1) has the form:

$$\Theta_1' = -\frac{Q_b}{\mu_b^2}\exp(-\mu_b\xi) + A'\xi + B';$$

$$\Theta_2' = \left(D' + \frac{Q_t}{2\beta}\xi\exp(\beta - \mu_b)\right)\exp(-\beta\xi);$$

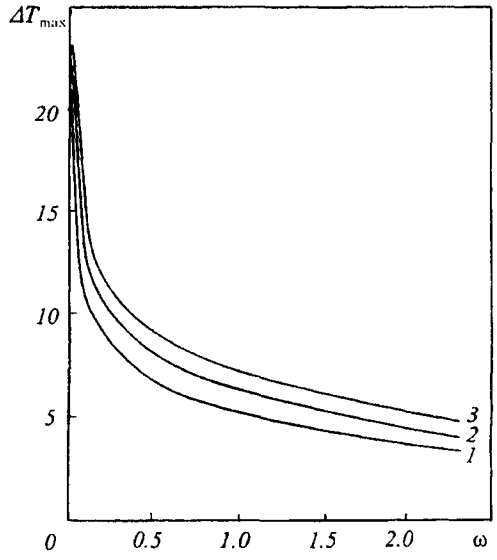
$$D' = \frac{\exp(\beta)}{\mathrm{Bi} + \beta\mathrm{Bi} + \beta}\left[\frac{Q_b}{\mu_b}\left(1 + \frac{\mathrm{Bi}}{\mu_b}\right) + \left\{\frac{Q_t}{2\beta} - \frac{1 + \mathrm{Bi}}{2}Q_t - \frac{1 + \mathrm{Bi}}{\mu_b}Q_b - \frac{Q_b\mathrm{Bi}}{\mu_b^2}\right\}\exp(-\mu_b)\right]; \qquad (5)$$

$$A' = \frac{\mathrm{Bi}}{1 + \mathrm{Bi}}\left[D'\exp(-\beta) + \left(\frac{Q_t}{2\beta} + \frac{Q_b}{\mu_b^2}\right)\exp(-\mu_b) - \frac{Q_b}{\mu_b}\left(\frac{1}{\mathrm{Bi}} + \frac{1}{\mu_b}\right)\right];$$

$$B' = \frac{A'}{\mathrm{Bi}} + \frac{Q_b}{\mu_b}\left(\frac{1}{\mathrm{Bi}} + \frac{1}{\mu_b}\right).$$

Figure 1 presents examples of the fields of the temperature increment in tissue $\Delta T(x)$ in PhDT as a function of the thickness of the layer of destroyed cells that is formed in this process and the system of blood circulation of the layer. For comparison, curve 1 gives the values of $\Delta T(x)$ in the absence of a tissue layer with a destroyed system of blood flow. It is obvious that at small L the difference in the increment of temperature of the two models with respect to ΔT is small; it increases with L and for typical $L \approx 5$ mm it may amount to ≈ 3°C. As I_0 increases, due to the destructive effects of PhDT, the appearance of an additional zone in which hyperthermal temperatures are created is quite possible.

We consider the dependence $\max_{\xi \geq 1}\Delta T(\xi)$ on blood flow for the zone where local hyperthermia can take place. It appears that $\Theta_2(\xi)$ for $\beta < \mu_t$ has a maximum at $\xi = \xi^*$



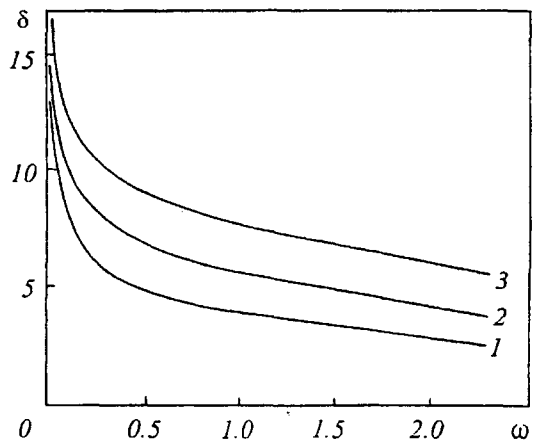


Fig. 2. Maximum temperature which can be attained in second layer as a function of blood flow: 1-3) calculated for values of L (mm) equal to 5, 3, 1, respectively. The other values are the same as in Fig. 1. ω, ml/(g·min).

Fig. 3. Interrelation of perfusion properties of tissue and depth of its heating in PhDT: 1-3) calculated for values of L (mm) equal to 1, 3, 5, respectively. The other values are the same as in Fig. 1. δ, mm.

$$\xi^* = \frac{\mu_t - \mu_b}{\mu_t - \beta} + \frac{1}{\mu_t - \beta} \ln \frac{Q_t \mu_t}{\beta D (\mu_t^2 - \beta^2)}. \tag{6}$$

For the case of (5), i.e., at $\beta = \mu_t$, $\Theta_2'(\xi)$ also has a maximum, but at $\xi = \xi^{*'}$:

$$\xi^{*'} = \frac{1}{\beta} - \frac{2\beta}{Q_t} D' \exp(\mu_b - \beta). \tag{7}$$

Using (6) and (7) we can determine the maximum value of ΔT by the following relations

$$\Delta T_{max} = T_0 \Theta_2(1) \quad \text{when} \quad \beta > \mu_t, \tag{8a}$$

$$\Delta T_{max} = \max \left\{ T_0 \Theta_2(1);\ T_0 \Theta_2(\xi^*) \right\} \quad \text{when} \quad \beta \le \mu_t. \tag{8b}$$

An analysis of relations (5) and (7) showed that at $\beta = \mu_t$ nothing radically new is revealed in the dependences $\Delta T(x)$, $\Delta T_{max}(\omega)$, and $\delta(\omega)$; all regularities are shown in Figs. 1-3. Calculations by (8) are, in particular, given in Fig. 2. It follows from the curves that the effect of tissue destruction in PhDT can additionally be associated with the attainment of not only hyperthermal, but even higher, thermotherapeutical temperatures. The developed model allows one to predict the profile of temperatures in a tumor with perfusion and when its optical properties are known.

For practical applications, not only possible profiles of temperatures in tissue but also estimations of the depths δ at which they are realized are of importance. We define δ such that $\Delta T(\delta) = \Delta T_{max}/e$, with δ being reckoned from $x = 0$. The dependences $\delta(\omega)$ show (Fig. 3) that the depths of tissue heating are determined, other quantities being equal, by the blood flow, the more substantially, the smaller it is. For brain tissue at the above-indicated values of ω, ε_{tt}, ε_{at}, and I_0, the increase in temperature ΔT amounts to (7–9)°C, and the depths of penetration to undamaged tissue are $(\delta - L) \approx 4$ mm.

Thus, it is shown that along with the process of photodynamic therapy, an increase in temperature that is capable of providing conditions of local hyperthermia and thermotherapy facilitates tissue destruction. It appears that this temperature mode can be created at a greater tissue depth as compared to that which is attained in PhDT.

It can be asserted that hyperthermia is an adjunct to PhDT, whose role is additionally reduced to localization of the heating mainly in the tumor or some part of it. This is explained by the fact that the zone of accumulation of photosensitizers is predominantly abnormal tissue and the laser radiation destroys a certain layer of it by changing its perfusion and optical properties. These changes, as is shown above, provide a specific temperature mode of cell damage of the remaining tumor or a part of it. Thus, if the tumor is surrounded by comparatively low-perfusion brain-tumor tissue [9] ($\omega \approx 0.05$ ml/(g·min), other conditions being equal, even thermotherapeutic temperatures ($\approx 55^{\circ}$C) can be attained, and $\delta \approx 15$ mm. This result has determined the development of radically new approaches to the destruction of brain tumors. They consist, basically, in the following: first, in the organization of a medical technology of PhDT which provides nearly hyperthermal temperature modes in malignant tissue; second, in providing conditions which reduce the perfusion characteristics of tumors, thus facilitating an increase in the volumes of destruction of them with nearby tissue being preserved; third, in the possibility of ensuring thermotherapeutic modes in tumors during PhDT. Implementation of these approaches can be attained by estimating the conditions of manifestation of them that are afforded by the suggested model. Additionally, it verifies the mechanisms and broadens the possibilities of PhDT itself and determines the conditions of conducting it in each specific case.

NOTATION

x, spatial coordinate; t, time; L, thickness of the destroyed layer; i, number of layer; ρ and c, density and specific heat capacity of tissue, respectively; ρ_b and c_b, density and specific heat capacity of blood; χ, coefficient of thermal conductivity; T, temperature; $\Delta T(x) = T(x) - T_0$; $T_0 = 37^{\circ}$C; α, coefficient of heat transfer; I_0, intensity of radiation at $x = +0$; ε_{ab}, ε_{at}, absorptions in blood and in the whole tissue, respectively; ε_{tb}, ε_{tt}, attenuations in blood and tissue, respectively; t_1, t_2, times of establishment of stationary modes in first and second layers; ω, blood flow. Subscripts: a, absorption; b, blood; t, attenuation.

REFERENCES

1. A. A. Krasnovskii, *Advances in Science and Technology, Modern Problems of Laser Physics*, Vol. 3 [in Russian], Moscow (1990), pp. 63-135.
2. I. S. Mel'nik, N. I. Bogachkov, and V. D. Rozumenko, *Techniques and Methodology of Photodynamic Therapy* [in Russian], Vols. 1-2, Kiev (1995). Deposited at State Scientific Engineering Library of Ukraine, No. 1971Uk95; No. 1972Uk95.
3. Z. P. Shul'man, B. M. Khusid, and I. V. Fain, *Inzh.-Fiz. Zh.*, **68**, No. 1, 75-85 (1995).
4. E. B. Chernyaeva, N. V. Stepanova, and L. L. Litinskaya, *Advances in Science and Technology, Modern Problems of Laser Physics*, Vol. 3 [in Russian], Moscow (1990), pp. 136-224.
5. B.W. Henderson, S. M. Waldow, W. P. Potter, and T. J. Dougherty, *Cancer Research*, **45**, 6071-6077 (1985).
6. J. Frietas, P. Pontiggia, F. Baronzio, and J. R. McZaren, *Adv. Exp. Med. Biol.*, **267**, 511-520 (1990).
7. L. O. Svaasand, Ch. J. Gomer, and E. Morinelli, *Future Directions and Applications in Photodynamic Therapy.* SPIE Institute Series, **IS6**, 233-248 (1990).
8. L. I. Grossweiner, *Laser in Surgery and Medicine*, **11**, 165-173 (1991).
9. Yu. A. Zosulya, *Blood Circulation in Tumors of Brain Hemispheres* [in Russian], Kiev (1972).