Tumor regression conditions under radiotherapy in the mathematical model with immune response

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Предложена модель роста опухоли с учетом иммунного контроля, которая допускает устойчивое состояние без опухоли. Для случаев однократного и фракционированного облучения получены критерии элиминации опухоли в явном виде. Аналитические зависимости между параметрами опухоли и параметрами терапевтического воздействия подтверждаются результатами численного моделирования.

We propose a model of tumor growth with immune control that admits a stable tumor-free state. We derive explicit tumor elimination criteria for both single and fractionated irradiation. The obtained analytical relationships between the tumor parameters and the parameters of radiotherapy are confirmed by numerical simulations.

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Introduction

The key goal of mathematical modeling of tumor growth is to optimize antitumor therapy and to predict not only short-term tumor shrinkage, but also durable regression or complete elimination. Classical nonlinear growth models (exponential and power-law growth, logistic, Gompertz, and Fisher-Kolmogorov-Petrovsky-Piskunov models) do not have a stable tumor-free state, or they can have only one stable positive state representing the carrying capacity [1]. While these models can fit experimental tumor growth data, they are poorly suited to simulate a successful treatment outcome. This motivates the development of new models in which the tumor-free state becomes stable under certain conditions.

The concept of cancer immunoediting provides the biological basis for such a model. Tumor-immune interaction is described by three phases: elimination (when the tumor cells are completely eliminated by the immune system), equilibrium (when the immune system controls tumor growth), and escape (when tumor cells evade this control) [2]. This concept assumes that elimination is possible and corresponds to a stable tumor-free state under sufficient immune effect.

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Model Equation

The model proposed in this paper describes not only tumor growth but also its potential suppression due to the immune response and radiotherapy. The tumor dynamics is represented by the following partial differential equation:

$$\frac{\partial u}{\partial t} = k\,\frac{\partial^2 u}{\partial x^2} - u\,(a-u)\,(1-u) - E\,(x,t)\,u, \tag{1}$$

where $u = u(x,t) \in [0,1]$ is the normalized tumor-cell density; diffusion with coefficient k models spatial invasion; $a \in (0,1)$ is a parameter taking into account the impact of the immune system on tumor dynamics; and $E(x,t)$ represents therapy exposure (single or fractionated irradiation).

The significant mathematical feature of this model without treatment ($E = 0$) is bistability of tumor dynamics: the stationary states $u = 0$ (tumor-free) and $u = 1$ (saturation) are stable, while $u = a$ is unstable. Hence, if the cell density u is below the threshold value a, the solution goes to zero, if above it, it tends to saturation.

Tumor Regression Conditions

Model equation (1) allows us to assess radiotherapy efficancy and to establish relations between exposure parameters and tumor parameters under which the immune system can eliminate the tumor after the exposure ends. Below, we consider the spatially uniform case when cell density u and external exposure E are independent of the coordinate x.

Let the single irradiation in (1) be modeled by a pulse of constant intensity $\mathcal{E}_0$ and duration τ:

$$E(t) = \mathcal{E}_0[\Theta(t-t_0) - \Theta(t-t_0-\tau)], \tag{2}$$

where $\Theta(x)$ is the Heaviside function, t_0 is the moment of the beginning of the exposure. During the pulse, the tumor dynamics is described by

$$\frac{\partial u}{\partial t} + u\,(a-u)\,(1-u) = -\mathcal{E}_0\,u. \tag{3}$$

If $\mathcal{E}_0 < \frac{(1-a)^2}{4}$, equation (3) has three roots: $u = 0$, u_1 and u_2 with

$$u_1 = \frac{1+a+\sqrt{(1-a)^2 - 4\mathcal{E}_0}}{2}, \quad u_2 = \frac{1+a-\sqrt{(1-a)^2 - 4\mathcal{E}_0}}{2}. \tag{4}$$

In this case, $u = 0$ and u_2 are stable, while u_1 is unstable (see Fig. 1(a)). If $\mathcal{E}_0 > \frac{(1-a)^2}{4}$, the equation (3) has only one root $u = 0$ which is stable.

The tumor will be eliminated if its density $u(t_0+\tau)$ at the end of the pulse is less than the immune threshold a. In the low-density approximation, the ($u \ll 1$) pulse equation (3) has a solution:

$$u = u_0\,\frac{a+\mathcal{E}_0}{u_0 + \delta\,\mathrm{e}^{(a+\mathcal{E}_0)(t-t_0)}}, \tag{5}$$

where $\delta = a + \mathcal{E}_0 - u_0 > 0$.

Solution (5) provides the condition for the parameters of the external exposure for the elimination condition $u(t_0 + \tau) < a$ in the form

$$\tau > \frac{1}{a + \mathcal{E}_0} \ln \frac{\mathcal{E}_0 u_0}{a\delta}. \tag{6}$$

It follows from (6) that the required exposure duration τ decreases with an increase of the intensity $\mathcal{E}_0$. A larger initial tumor density u_0 requires a longer exposure time τ.

Next, we investigate fractionated irradiation. Let it have the form of N pulses of the same constant amplitude $\mathcal{E}_0$, having the same duration τ and separated by the same intervals τ_0:

$$E(t) = \mathcal{E}_0 \sum_{n=1}^{N} [\Theta(t - t_0 - (n-1)(\tau + \tau_0)) - \Theta(t - t_0 - (n-1)\tau_0 - n\tau)]. \tag{7}$$

Then, assume that the external exposure satisfies the balance condition: the value of the density $u(t)$ at the start of a pulse is equal to its value at the beginning of the next pulse. Approximating the time derivative in equation (3) by the ratio of finite differences yields equality

$$(u(a-u)(1-u) + \mathcal{E}_0 u)\tau + u(a-u)(1-u)\tau_0 = 0, \tag{8}$$

which defines quasi-stationary levels of tumor cell density during fractionated therapy. The critical value of intensity

$$\tilde{\mathcal{E}}_l = \left(1 + \frac{\tau_0}{\tau}\right) \frac{(1-a)^2}{4} \tag{9}$$

determines the number of stable states of the system.

If $\mathcal{E}_0 < \tilde{\mathcal{E}}_l$, equation (8) has three roots $u = 0$, $u = \tilde{u}_1$ and $u = \tilde{u}_2$, where

$$\tilde{u}_1 = \frac{1 + a + \sqrt{(1-a)^2 - 4\mathcal{E}_a}}{2}, \quad \tilde{u}_2 = \frac{1 + a - \sqrt{(1-a)^2 - 4\mathcal{E}_a}}{2}. \tag{10}$$

Here $\mathcal{E}_a = \frac{\tau}{\tau + \tau_0} \mathcal{E}_0$, that has a sense of the average value of the external impact over the interval $\tau + \tau_0$.

If $\mathcal{E}_0 > \tilde{\mathcal{E}}_l$ equation (8) has only one stable state $u = 0$, and if the number of fractions is sufficient, we can achieve tumor elimination for any initial cell density (Fig. 1(b)).

Let us estimate the number of fractions required to achieve tumor elimination by the end of treatment. Because the growth rate $f(u) = -u(a-u)(1-u)$ is nonlinear, we partition the interval $a < u < 1$ into three subregions and apply an appropriate approximation for each of them, and then sum the contributions depending on the initial density.

For the first region ($a < u < u_e$, the value of u_e will be defined below), we use the low density approximation again. Equations for the exposure and recovery phases are

$$\frac{du}{dt} = -\mathcal{E}_0 u, \quad \frac{du}{dt} = -u(a-u). \tag{11}$$

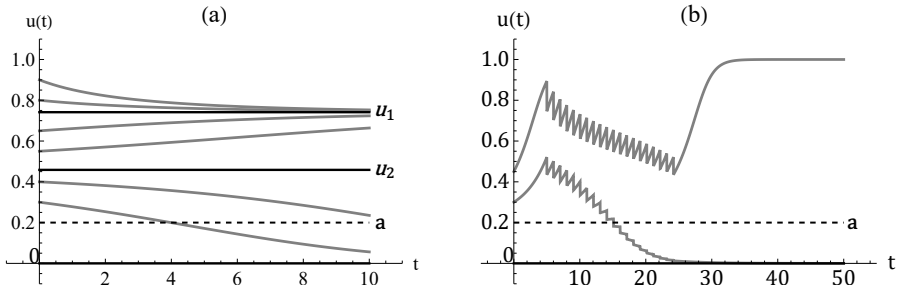


Fig. 1. Integral curves of solutions of the model equation (3) in the spatially uniform case $u = u(t)$ for single (a) and fractionated (b) irradiation.

Using the induction method, we obtain the formula for the density after the Nth fraction:

$$\tilde{U}_N = \frac{a u_0 \mu^{-1}(1-\mu\eta)}{a(\mu\eta)^{N-1}(1-\mu\eta) + (1-\eta)[1-(\mu\eta)^{N-1}]u_0}, \tag{12}$$

where $\mu = e^{\mathcal{E}_0 \tau}$ and $\eta = e^{a\tau_0}$.

The variable u will tend to zero by the end of the Nth fraction if the condition $\tilde{U}_N < a$ is satisfied. From this, we can estimate the necessary number of fractions N_1:

$$N_1(u_0) > \frac{1}{\mathcal{E}_0\tau + a\tau_0} \ln\left[\frac{u_0(\mu-1)}{a(\mu-1/\eta) + u_0(1/\eta-1)}\right]. \tag{13}$$

The applicability limit of formula (13) is given by the zero of the denominator in the logarithm: $u_{th} = \frac{a(\mu\eta-1)}{\eta-1}$. As the right boundary of the first region, we take the average value $u_e = \frac{u_{th}+a}{2}$.

As the right boundary of the second region ($u_e < u < u_{max}$), we take the point u_{max} at which the growth rate function $f(u)$ takes its maximal value. Here, we use the average values of density $\overline{u}$ in this region and change of density $\overline{f}$:

$$\overline{u} = \frac{u_0 + u_e}{2}, \quad \overline{f} = \frac{1}{u_0 - u_e}\int_{u_e}^{u_0} f(z)dz, \tag{14}$$

and determine the number of fractions required to reduce the density from u_0 to some u_e as

$$N_2(u_0) > \frac{u_0 - u_e}{\mathcal{E}_0\tau\overline{u} - \overline{f}(\tau+\tau_0)}. \tag{15}$$

For the third region ($u_{max} < u < 1$), it was found that a constant value $f^* = f(u_{max})$ provides the best approximation of the density change. The equations for the exposure and recovery phases read as

$$\frac{du}{dt} = f^* - \mathcal{E}_0 u, \quad \frac{du}{dt} = f^*. \tag{16}$$

The formula for the tumor cell density U_N after the Nth exposure-recovery phase has the following form:

$$U_N = \mu_2 u_0 + \frac{1-\mu_2^N}{1-\mu_2}\left(\tau_0 + \frac{1-\mu_2}{\mathcal{E}_0}\right) f^*. \tag{17}$$

The number of exposure-recovery cycles required to reach the level u_{max}:

$$N_3(u_0) > \frac{1}{\ln \mu_2} \ln \frac{[(1-\mu_2)u_{max} - \tau_0 f^*]\mathcal{E}_0 - (1-\mu_2)f^*}{[(1-\mu_2)u_0 - \tau_0 f^*]\mathcal{E}_0 - (1-\mu_2)f^*}. \tag{18}$$

The obtained analytical estimates demonstrate correct relationships between the parameters of therapy and the tumor, which confirms the adequacy of the proposed model and is consistent with the results of numerical modeling.

Conclusion

A mathematical model of tumor growth taking into account the interaction of tumor cells with the immune system and external therapeutic effects is proposed. This model reproduces the key biological features of tumor growth and its interaction with the immune system (suppression of tumor growth, tumor equilibrium state, escape of immune control).

Two variants of radiotherapy have been investigated: single and fractionated exposure. The relationships between the tumor parameters (initial cell density u_0 and immune threshold a) and the parameters of radiotherapy (intensity $\mathcal{E}_0$ and duration of exposure τ, duty cycle and number of fractions N), at which tumor suppression is achieved, were revealed.

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Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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