Understanding tumour dynamics in vivo: The potential of kinetic models in radio-oncology

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Abstract
To facilitate the investigation of the tumour response onto radiation therapy in vivo, a modified kinetic LQ-model is developed. It is based on a dose quantity which is considered as proportional to cellular damage. The resulting differential equations are implemented in a computer program and solved numerically. The model is in agreement with the kinetic model of Carlone. In contrast to the model of Carlone and other models focussing DNA lesion kinetics, different aspects of tissue dynamics (e.g. repopulation, oxygenation) can be integrated directly in the proposed LQ-based model.

1. Introduction

In vivo tumour response to ionizing radiation can differ remarkably from the response observed in vitro. This difference may be based on several processes related to the interaction of tumour cells with tumour environment (e.g. endothelial cells and tumour vasculature [1]). Also immune reactions and the related inflammatory processes may have an important influence. The adaption of radiobiological models based on the observation of clonogenic survival in vitro (e.g. the LQ model) to the situation in vivo is difficult. Repair, repopulation, interaction with host tissue, influence of radiotherapy onto vasculature and oxygenation can be described by the rates of changes of the related quantities (population size, cell densities, concentrations etc.). This approach directly leads to kinetic models using differential equations. Kinetic models are used for modeling DNA-lesion kinetics and repair [2,3], early tissue reactions [4] or the risk of radiation induced cancer [5]. Probably, it may be difficult to solve the resulting differential equations analytically under certain conditions. This problem can be avoided by using numerical integration. We investigated a modified kinetic LQ model which has a high degree of flexibility for extensions and may therefore be a basis for better understanding of tumour dynamics in vivo. Two different models for tumour cell repopulation were compared here.

2. Materials and Methods

The proposed model is based on an ordinary differential equation for tumour population size, which is corresponding to the LQ-model. Assuming no change of cellular repair (low dose rate) and no repopulation of tumour cells, the change (reduction) of the size of an irradiated population is depending on the numbers of tumour cells $N_1 = N_1(t)$ itself, the dose rate $R = \dot{D}$ (which is the first derivative of the dose $D = D(t)$ in respect to the time) and a radio-sensitivity coefficient α :

$$\frac{dN_1}{dt} = -\alpha N_1 \cdot R = -\alpha N_1 \cdot \frac{dD}{dt} \qquad (1)$$

The solution of Eq. (1) is $N_1(D) = N_0 \cdot e^{-\alpha D}$. The extension to higher doses and higher dose rates can be realised by a second, dose-depending term using a coefficient 2β:

$$\frac{dN_1}{dt} = -\left(\alpha + 2\beta D\right) \cdot R \cdot N_1 \qquad (2)$$

Separation and integration over dose results in $N_1(D) = N_0 \cdot e^{-(\alpha D + \beta D^2)}$. The natural logarithm of surviving fraction $S = N_1 / N_0$ is given by $\ln S = -(\alpha D + \beta D^2)$. This is corresponding to the LQ-model.

Regarding the tumour volume, lethally damaged cells are not eliminated immediately. Therefore, a second cell population N_2 is introduced, which is reduced by first order kinetics using the kinetic constant k_{res}:

$$\frac{dN_2}{dt} = \frac{dN_1}{dt} - k_{res} N_2 \qquad (3)$$

For inclusion of dose and time dependent change of cellular repair and repopulation, Eq. (2) is modified. First, the (physical) dose is substituted by a biological dose quantity Γ_{i1}, which is representing a biological active proportion of the applied dose. The index *i* corresponds to the biological process which is linked to the biological dose quantity Γ_{i1}. Here, *i* = 1 is corresponding to cellular repair processses. The second modification is concerning the inclusion of repopulation by an additional term describing the tumour growth model using a dose and population size depending function $f(N, \Gamma_{21})$:

$$\frac{dN_1}{dt} = -(\alpha + 2\beta\Gamma_{11}) \cdot R \cdot N_1 + f(N_1, \Gamma_{21}) \qquad (4)$$

In a first step, it is assumed, that Γ_{11} is different to Γ_{21}. The two quantities may not be independent from each other since repair of cellular damages and cell division are coupled processes.

The quantities Γ_{i1} are determined by the following kinetic model when assuming first order repair kinetics:

$$\frac{d\Gamma_{i1}}{dt} = R - \gamma_i \cdot \Gamma_{i1} \qquad (5)$$

$$\frac{d\Gamma_{i2}}{dt} = \gamma_i \cdot \Gamma_{i1} \qquad (6)$$

The kinetic constants γ_i may be different for repair ($i=1$) and repopulation ($i=2$), but the two constants may be coupled. Regarding Eq.(5) and (6), the following condition is fulfilled: $\lim_{t\to\infty}\left[\Gamma_{i2}(t)\right]=\lim_{t\to\infty}\left[D(t)\right]=D_{tot}$. The impact of hypothetical quantities Γ_{i1} onto the cells is mediated by the radiosensitivity constant β at one hand and by $f(N,\Gamma_{21})$ at the other hand. Here, a repopulation model using a dose independent repopulation term $k_N \cdot N_1$ with constant k_N is compared with the following dose dependent function describing the radiation induced inhibition of the rate of growth:

$$f(N,\Gamma_{21})=\frac{k_{R1}}{(1+k_{R2}\cdot\Gamma_{21})}\cdot N=k_N(\Gamma_{21})\cdot N \qquad (7)$$

For an irradiation with constant dose rate *R*, the dose quantities Γ_{i1} reach a steady state level Γ_{i1eq}. The condition for steady state is given by:

$$\Gamma_{i1eq}=\frac{R}{\gamma_i} \qquad (8)$$

If the repopulation term is neglected, the logarithm of surviving fraction becomes constant at high doses (when reaching the equilibrium):

$$\left[\frac{d\ln S}{dD}\right]_{\Gamma_1\to\Gamma_{1eq}}=-(\alpha+2\beta\Gamma_{11eq}) \qquad (9)$$

Therefore, the model is exhibiting a linear-quadratic-linear behaviour as observed for high fraction doses [6]. The model was compared to existing kinetic radiobiological models. The proposed kinetic LQ-model without repopulation leads to identical results as the model of Carlone [3], when the kinetic constant γ_1 is adapted to the dose rate using the relation $\gamma_1=\mu+p\varepsilon R$. The constant *p* is defined as the yield per unit dose of sub-lethal lesions [7] and *R* is the dose rate (as above). In the model of Carlone, pre-existing sublethal lesions can interact with the formation of new lesions with the interaction probability ε. The relation to the constant for radiosensitiyity β is given by $\beta=p^2\varepsilon$.

The differential equations Eq. (3), (4), (5) and (6) were implemented in a computer program using a Runge-Kutta algorithm. Also the kinetic model of Carlone et al. [3] was implemented. The surviving fractions as function of dose or time and the resulting TCP's for both models can be compared directly. Different therapy modalities were investigated. Also different approaches for repopulation were tested.

3. Results

For biologically targeted radionuclide therapy, the kinetic LQ-model is in agreement to classical LQ calculations [8]. For fractionated RT, the proposed model also is in agreement with the compartmental model of Carlone, even when the quantity Γ_{11} is far away from the equilibrium. Fig.1 shows the impact of Γ_{11} onto the logarithm of surviving fraction. The case $\gamma_1 = 0$ d^{-1} is corresponding to the common LQ formalism. With increasing value for γ_1, the final slope becomes flatter and a linear-quadratic-linear behavior is exhibited.

For all simulations, the parameters for radio-sensitivity are chosen as $\alpha = 0.3$ Gy^{-1} and $\beta = 0.05$ Gy^{-2} respectively.

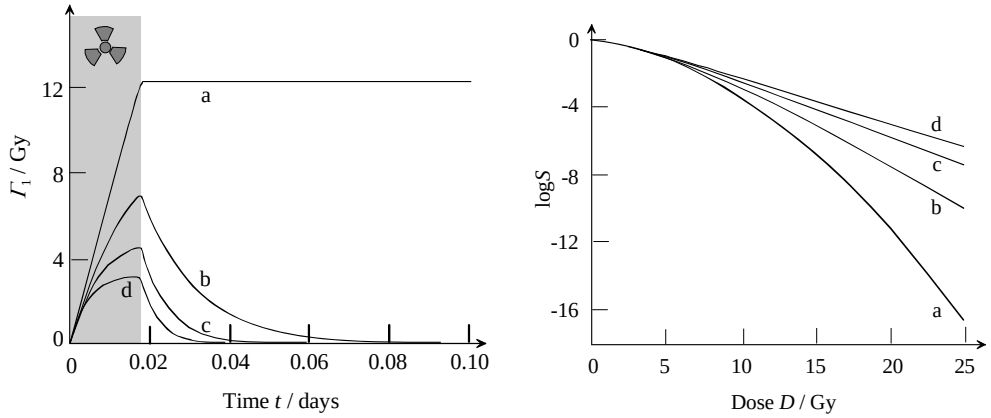

Fig.1. Relation between Γ_{11} and log$S$: Left Diagram shows the temporal development of $\Gamma_1 = \Gamma_{11}$ for a fraction of D = 12.5 Gy. Right diagram shows the logarithm of surviving fraction for a single fraction. The parameters are the following: (a) $\gamma_1 = 0$ d^{-1}; (b) $\gamma_1 = 70.22$ d^{-1}; (c) $\gamma_1 = 140.45$ d^{-1}; (d) $\gamma_1 = 210.67$ d^{-1}; no repopulation ($k_N = 0$ d^{-1}), calculated with Runge-Kutta method with $\Delta t = 0.5 \cdot 10^{-6}$ d.

Referring to Eq. (7), the influence of Γ_{21} onto $k_N(\Gamma_{21})$ is showed in Fig.2 for different values of k_{R2}. The comparison between the different models for repopulation is demonstrating the effect of growth delay due to radiation (Fig.3). In this model, a remarkable growth delay can be produced only by a reasonably large value for k_{R2} (above 4.0 Gy^{-1}, Fig.2. curve *e*). In addition, the effect is only prominent for a relatively slow repair process and therefore for a small constant γ_2 (comparable to k_{R1}, which may be considered as intrinsic growth constant). For the illustrated case in Fig.3, γ_2 is set to 2 d^{-1}. The volume reduction (Fig.3) is also depending on the rate of tissue resorption. The larger the value for k_{res} the stronger the visible effect onto the difference curves of the tumour volume and the logarithm of surviving fraction (Fig.3).

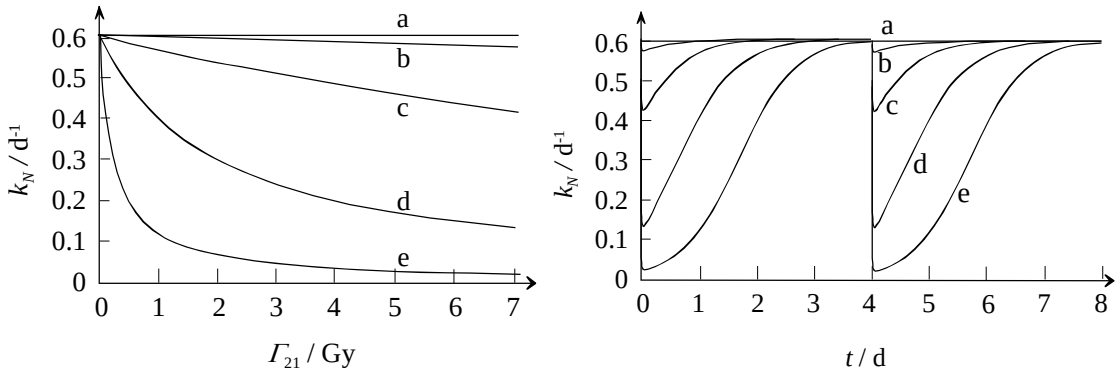

Fig.2. Dose-dependency of k_N: Left Diagram shows the Γ_{21} - dependency of k_N; Right diagram shows the temporal development of $k_N(\Gamma_{21})$ for two fractions of 7 Gy. Parameters: $k_{R1} = 0.6$ d^{-1}; $\gamma_1 = 163.2$ d^{-1}, $\gamma_2 = 2$ d^{-1}; (a) $k_{R2} =$ 0.0 Gy^{-1} (corresponding to the model with a constant value for k_N); (b) $k_{R2} = 1.0$ Gy^{-1}; (c) $k_{R2} = 2.0$ Gy^{-1}; (d) $k_{R2} = 3.0$ Gy^{-1}; (e) $k_{R2} = 4.0$ Gy^{-1}

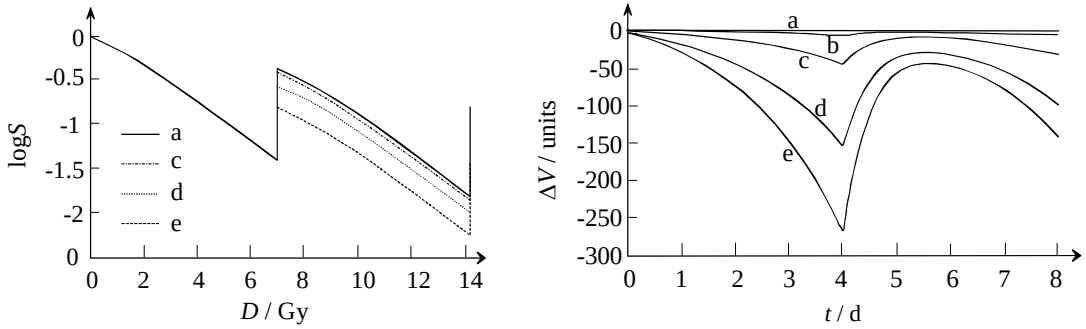

Fig.3. Impact of radiation depending k_N onto tumour size: Left Diagram is showing the logarithm of survival as function of dose *D*, same parameters as in Fig.2. Right: Temporal development of the difference ΔV of tumour volume *V* (normalized to 1000 units) between dose independent and dose dependent growth constant k_N, the necrotic cells N_2 are also included ($k_{res} = 2$ d^{-1}).

4. Conclusions

The kinetic formulation of the LQ-model offers a high degree of flexibility for extensions to repair, repopulation and different therapy modalities. For the tested cases, the proposed model is in agreement with existing radiobiological models also for high dose rates and doses. Extensions to arbitrary dose distributions can be implemented in a very efficient way and provide additional information for optimizing radiotherapy. The proposed model allows the quantitative analysis of

growth delay of tumours under treatment. Calculations using the presented model suggest that a growth delay is only observable in the experiment for a strong dose dependence of the growth constant k_N.

The system can be explored by plotting the logarithm of surviving fraction and the tumour volume versus dose or time. Therefore, the computer simulation also may be used for educational purpose (e.g. to learn about effects of hyper- or hypo-fractionation).

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