Computer simulation of oxygenation and growth inhibition of tumours during fractionated radiotherapy: Exploration of the dynamic system behaviour

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Purpose: Kinetic models can provide the exploration of the dynamics of the tumor system including the effects caused by the vascularture. The presented model was used to explore the impact of oxygenation on the tumor volume and tumor control probability (TCP) during fractionated radiotherapy using high fraction doses (e.g. 3x20 Gy for stage I NSCLC).

Methods: The response of the tumor upon ionizing radiation (photons) is modeled by a kinetic LQ-model [1]. The influence of oxygenation on the parameters for radio-sensitivity is implemented following a model of Wouters and Brown [2]. Our proposed model includes tumor oxygen consumption, vascular oxygen support, oxygen dependent repopulation of tumor cells and degradation of lethally damaged cells (see flow chart Fig.1). The concept of the kinetic LQ-model is applied to both, the endothelial cell population and tumor cells. It is assumed, that the endothelial cell repopulation is governed by the pO2 - level (mediated by e.g. VEGF). The resulting differential equations are implemented in a computer program, which calculates logarithm of surviving cell fraction, tumor volume and TCP.

Results: Different simulations with varying radio-sensitivity coefficients for endothelial cells and tumor cells have been carried out (1-6 fractions with 10-35 Gy per fraction). For high radio-sensitivity of endothelial cells compared to the tumor cells, the variation of radio-sensitivity coefficients for endothelial cells has only a small impact on TCP. The slower the degradation of lethally damaged endothelial cells the better is the TCP (due to better oxygenation). Strong variations of the oxygenation can be observed after the first fraction (e.g. Fig.2) over a wide range of the parameter space. For subsequent fractions, the tumor remains in normoxic or hypoxic milieu, depending on the ratio of tumor cells to endothelial cells and the elimination rate of lethally damaged tumor and endothelial cells.

Conclusion: This kinetic model demonstrates a strong impact of kinetic constants for tissue degradation after irradiation. The common LQ – model could be replaced for large fractions > 10 Gy by a kinetic model which includes degradation of the vascular system. The proposed model can be used as a theoretical framework, which should be tested and adapted by comparison with in-vivo data.

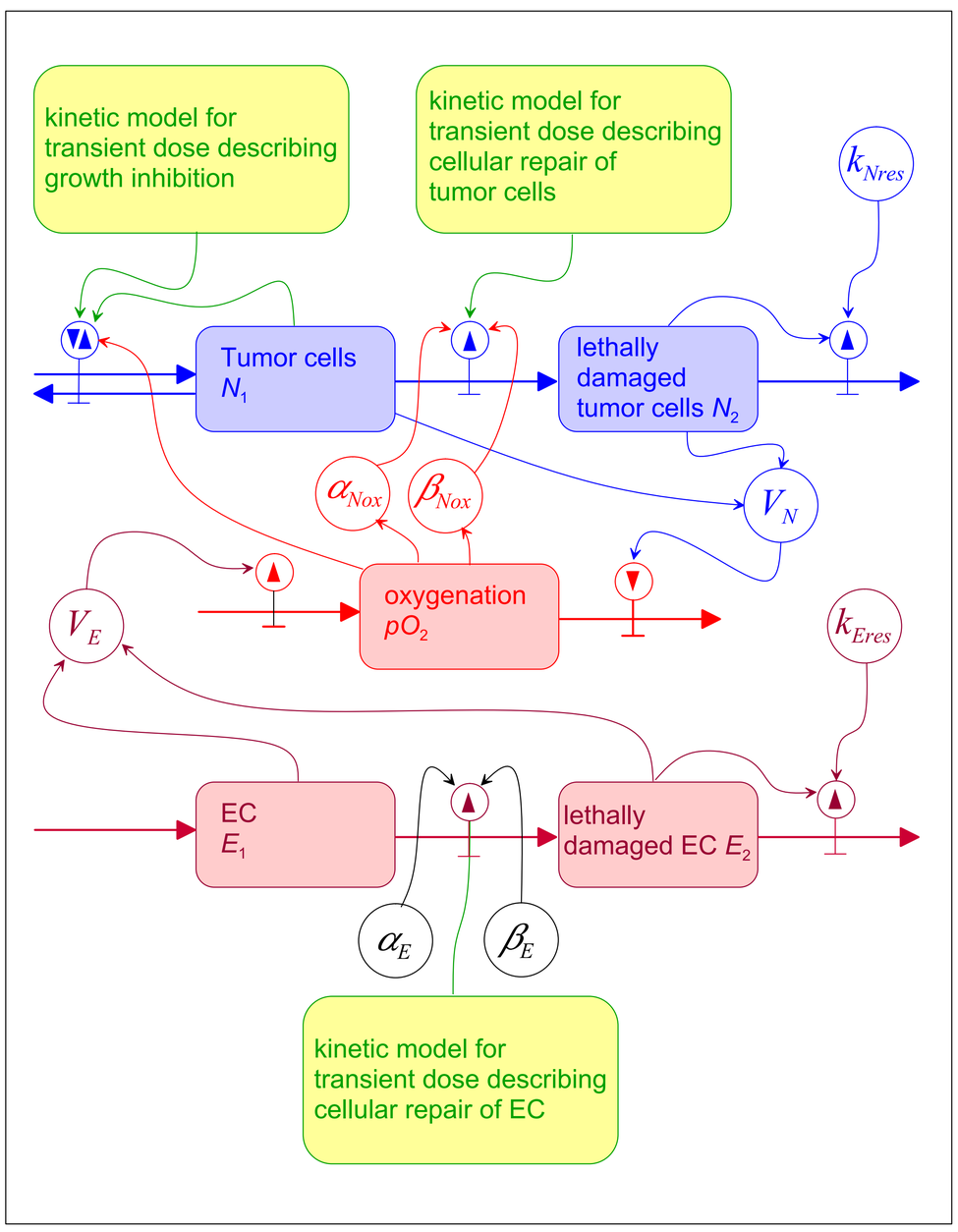

Fig.1. Simplified flowchart of the model: V_E is the volume of vasculature, V_T the volume of the tumour, k_{Eres} is a constant describing the speed of tissue degradation of irradiated vessels and k_{Nres} a constant describing the speed of metabolic inactivation of tumour cells. For both processes, first order kinetics is assumed. The radio-sensitivity coefficients α_E and β_E for the endothelial cells are estimated from Rhee et al. [3].

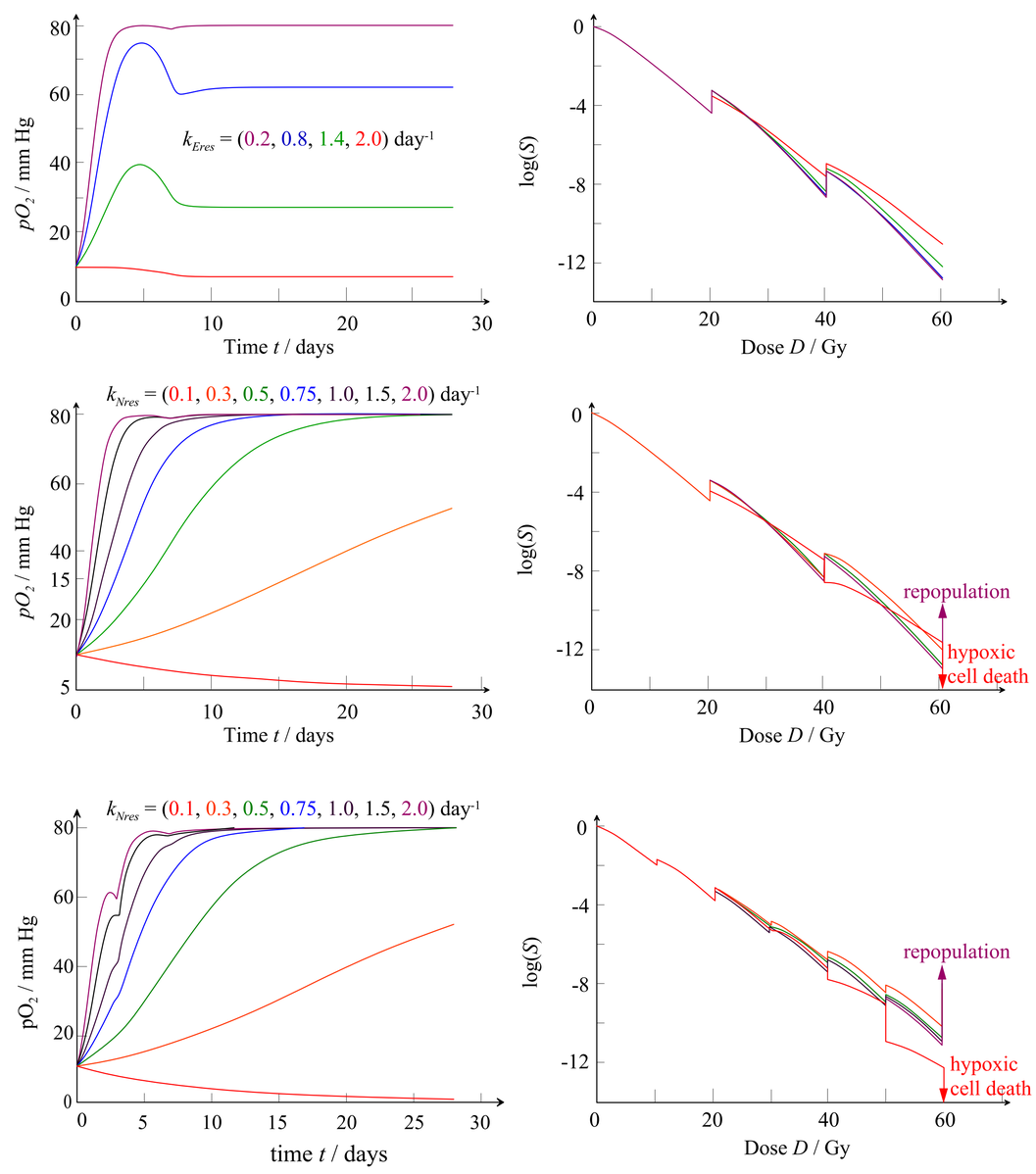

Fig.2. Impact of a fractionated radiotherapy onto oxygenation (pO_2 – level, left) and logarithm of surviving fraction (ln$S$, right) for adenocarcinoma for the following cases: upper diagrams 3 x 20 Gy and varying tissue degradation constant for endothelial cells (k_{Eres}); middle diagrams 3 x 20 Gy and varying constant for metabolic inactivation of tumour cells (k_{Nres}); lower diagrams 6 x 10 Gy with varying constant for metabolic inactivation of tumour cells (k_{Nres}).
High values for k_{Eres} (fast inactivation / loss of function of vasculature after irradiation compared to metabolic inactivation of tumour cells) results in moderate hypoxic condition but no hypoxic cell killing appears, ln$S$ is mainly influenced by oxygen dependent α_{Nox} and β_{Nox}.
Low values for k_{Nres} (slow metabolic inactivation of tumour cells after irradiation compared to degradation of vessels) results in hypoxic milieu which is responsible for hypoxic cell killing (visible as steep decay of ln$S$ after irradiation). This effect overcompensates the loss of radio-sensitivity in the case of 3 x 20 Gy and 6 x 10 Gy respectively. For increasing values of (k_{Nres}), the effect of reduced radio-sensitivity due to hypoxic condition (orange curve) and the radio-sensitizing effect (green and violette curve) become visible . For high values of k_{Nres}, the cell killing between 3 x 20 Gy and 6 x 10 Gy is different an dose rate dependent (dose rate R = 825 Gy/d for 6 x 10 Gy and R = 1650 Gy for 3 x 20 Gy).

References:
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