

Quantitative Modeling of Tumor Dynamics and Radiotherapy

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Abstract Cancer is a complex disease, necessitating research on many different levels; at the subcellular level to identify genes, proteins and signaling pathways associated with the disease; at the cellular level to identify, for example, cell-cell adhesion and communication mechanisms; at the tissue level to investigate disruption of homeostasis and interaction with the tissue of origin or settlement of metastasis; and finally at the systems level to explore its global impact, e.g. through the mechanism of cachexia. Mathematical models have been proposed to identify key mechanisms that underlie dynamics and events at every scale of interest, and increasing effort is now being paid to multi-scale models that bridge the different scales. With more biological data becoming available and with increased interdisciplinary efforts, theoretical models are rendering suitable tools to predict the origin and course of the disease. The ultimate aims of cancer models, however, are to enlighten our concept of the carcinogenesis process and to assist in the designing of treatment protocols that can reduce mortality and improve patient quality of life. Conventional treatment of cancer is surgery combined with radiotherapy or chemotherapy for localized tumors or systemic treatment of advanced cancers, respectively. Although radiation is widely used as treatment, most scheduling is based on empirical knowledge and less on the predictions of sophisticated growth dynamical models of treatment response. Part of the failure to translate modeling research to the clinic may stem from language barriers, exacerbated by often esoteric model renderings with inaccessible parameterization. Here we discuss some ideas for combining tractable dynamical tumor growth models with radiation response models using biologically accessible parameters to provide a more

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intuitive and exploitable framework for understanding the complexity of radiotherapy treatment and failure.

Keywords Mathematical model · Cellular automaton · Radiotherapy · Accelerated repopulation · cancer stem cells

1 Radiotherapy

Radiotherapy is a common treatment for cancer, either alone or in combination with surgery. The aim of radiotherapy is to destroy cancer cells with radiation while limiting the damage to nearby healthy cells (Oldham 2001). If tumor cells respond to irradiation at lower doses than normal tissue, then a therapeutic window exists in which a variety of treatment protocols can be used to eradicate the tumor while sparing normal tissue. However, if tumor and normal tissue respond similarly to irradiation a therapeutic window may be nonexistent. Ionizing particles interact with the genetic material of the cells, which disables their growth and division functions by breaking chemical bonds. These lethal events are either single- or double-hit events in the nuclear DNA. A lethal single-hit event results from the misrepair of one or more sublethal DNA lesions created by a single particle track, whereas a lethal double-hit event results from the nonviable combination of two sublethal DNA lesions created by two radiation particle tracks (Dale 1996). Each 1 Gy (1 Gy = 1 Gray = 1 Joule/kg) dose of gamma radiation damages about 2,000–4,000 bases in a DNA strand, causes about 1,000 sub-lethal single-strand breaks, and about 20–25 double-strand breaks (Turesson et al. 2003) (Fig. 1). Sub-lethal damage is repairable with time (i.e. 60–70 min (Brenner et al. 1998; Guerrero and Allen Li 2003)), so the number of cells

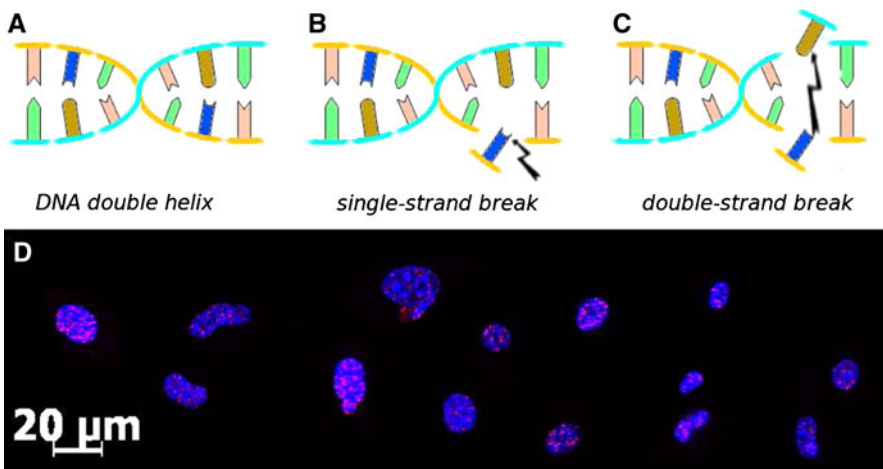


Fig. 1 Schematic diagram of the DNA double helix with different base pairs (a), radiation induced single- strand break (b) and double-strand break (c) (Modified from Enderling et al. 2008). (d) Examples of radiation induced DNA double strand breaks in GL261 glioma cancer cells after irradiation with 5 Gy. Red dots are foci of DNA repair protein 53BP1

that survive after such damage is highly dependent on the dose rate (Dale 1996). DNA double-strand breaks are repaired either by homologous recombination or non-homologous end-joining (Sancar et al. 2004), and cell killing is defined as the number of un- or misrepaired double-strand breaks. Radiation-induced DNA double strand breaks can be visualized using markers for DNA repair proteins, e.g. 53BP1. Figure 1d shows an example of radiation-induced DNA repair foci indicative of DNA double strand breaks in GL261 glioma cancer cells after irradiation with 5 Gy. Despite the steady increase in our molecular knowledge of the cancer cell, most treatment strategies, including radiotherapy, do not affect cancer cells uniquely but all proliferating cells. Radiotherapy is successful because host cells are for the most part non-proliferative and have better repair mechanisms than tumor cells (Oldham 2001).

2 The Linear-Quadratic Model of Radiotherapy

Cell survival after exposure to radiation depends on the efficacy of DNA damage repair. Cell death is triggered when double-strand breaks remain un- or misrepaired. However, only 1–2% of all radiation induced double-strand breaks are really lethal (Turesson et al. 2003). Radiation can induce DNA double strand damage either by one-track actions in which both strands of the DNA are directly damaged, or by two independent track induced DNA double strand breaks that are combined to form a misrepaired lesion. The established model to calculate the probability of cell survival S after n fractions of irradiation with dose d is the so-called linear-quadratic (LQ) model:

$$S = e^{-nd(\alpha + \beta d)} \tag{1}$$

where α and β are cell-specific radiosensitivity parameters. Figure 2 shows the dose-dependent survival probabilities for cells with different radiosensitivities and emphasizes the importance of reliable estimation of those sensitivity parameters.

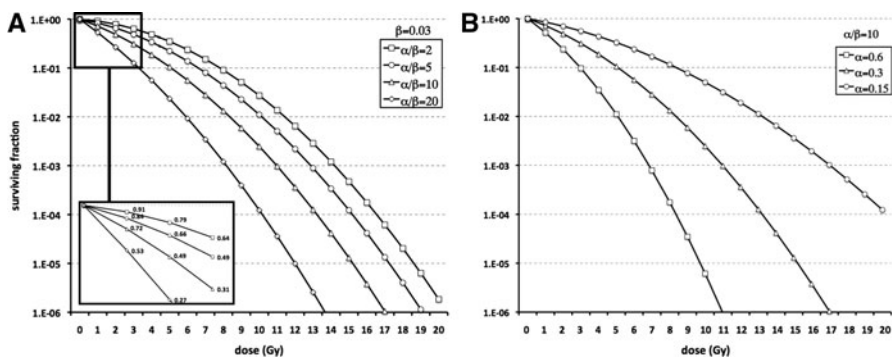


Fig. 2 a Dose-dependent survival fraction for tumors or tissues with different α/β radiosensitivities for constant $\beta = 0.03$. b α and β dependent radiation response for tumors with $\alpha/\beta = 10$

Detailed descriptions of the linear-quadratic and tumor control probability models (Gonzalez and Carando 2008) and several developments can be found in a recent review (O’Rourke et al. 2009). Although the LQ model is extensively used it has significant shortcomings. The five *R*’s of fractionated radiotherapy—*Repair*, *Re-population*, *Re-distribution* (in the cell cycle), *Re-oxygenation* and (intrinsic) *radioResistance* (Steel et al. 1989; Withers 1975)—are not sufficiently incorporated, although some extensions to the LQ model have been made to include some of the *R*’s (Brenner 1995; Little 2007) or population heterogeneity (Hlatky et al. 1994).

One feature unaccounted for is the relative resistance of non-cycling cells, which is often amplified by their sub-normoxic status. On the other hand, during consecutive fractions of radiation, actively dividing cells die off, and previously quiescent cells can become exposed to oxygen and nutrients again and start to proliferate. Indeed, quiescence and repopulation have been identified as the crucial factors for treatment failure (Kim et al. 2005). Although tumor repopulation can be accounted for in the LQ model through a simple ‘ $+\lambda T$ ’ inclusion in the exponent, this only approximates the complicated dynamics of tumor cell repopulation between consecutive treatment fractions. Multi-compartment models have been utilized extensively to describe tumor growth dynamics, and straightforward extensions can be made to include cell loss due to radiation.

3 Continuous Tumor Growth Models and Radiotherapy

Modeling tumor growth with continuous population models has a long history [reviewed in (Araujo and McElwain 2004; Lowengrub et al. 2009)]. The spatio-temporal dynamics of a population of cancer cells, c , is successfully described by a growth and death term, spatial displacement and cell motility, and interactions with the host f

$$\frac{\partial c}{\partial t} = \overbrace{\lambda(c)c}^{\text{cell proliferation}} - \overbrace{\delta(c)c}^{\text{cell death}} + \overbrace{\phi \nabla^2 c}^{\text{random motility}} - \overbrace{\psi \nabla \cdot (c \nabla f)}^{\text{taxis}} \tag{2}$$

where ϕ and ψ represent tumor-specific random motility and taxis coefficients, and $\lambda(c)$ and $\delta(c)$ are cell proliferation and cell death functions that describe frequently assumed exponential, logistic or Gompertz growth patterns. Effects of radiation on a tumor population can be included in such models by adding a loss term $R(\alpha, \beta, d, t)$ that describes the cell loss due to radiation with dose d at time t for cells with radiosensitivity parameters α and β (Rockne et al. 2009):

$$\frac{\partial c}{\partial t} = \lambda(c)c - \delta(c)c + \phi \nabla^2 c - \psi \nabla \cdot (c \nabla f) - \overbrace{R(\alpha, \beta, d, t)c}^{\text{radiotherapy}}. \tag{3}$$

As alluded to above, successful modeling of radiation effects requires knowledge of the radiosensitivity parameter α (/Gy) and β (/Gy²). For many tumors the α/β ratio is estimated or known from empirical observations. In a recent study, Rockne and co-workers have elegantly shown how mathematical models can help estimate the range of those parameters (Rockne et al. 2009). The authors extended a well-established and parameterized model of glioma growth dynamics (Swanson et al. 2000, 2002, 2007, 2008) to include radiotherapy response:

$$\frac{\partial c}{\partial t} = \overbrace{\nabla \cdot (\phi \nabla c)}^{\text{net dispersal}} + \overbrace{\lambda_c c}^{\text{net proliferation}} - \overbrace{R(\alpha, t)c}^{\text{loss due to radiotherapy}} \quad (4)$$

where c is the density of the glioma cell population. Once the tumor has reached a size that corresponds to the average clinical presentation (10–20 mm radius) a clinically established radiation protocol is simulated. Assuming a constant ratio of $\alpha/\beta = 10$, the model can simulate the tumor response to treatment for different α values. The residual tumor mass after treatment is then compared to the typical response window in the clinic, which allows an estimation of the radiosensitivity range of glioma cells (Fig. 3). Because this model is completely parameterized by clinical data, it allows for the simulation of virtual trials. Ignoring tissue toxicity effects, the model can compare the standard treatment protocol with accelerated or decelerated schedules on the virtual tumors. Among other things, the model shows that delivering a total dose D in $n = 5$ fractions with $d = D/5$ on consecutive days yields maximum tumor suppression, whereas a protocol where D is delivered as a single dose ($n = 1$) provides the poorest outcome.

The strength of the Rockne model (Rockne et al. 2009) is arguably the small number of parameters in a well-parameterized model. The parameters are obtained directly from patient data using combinations of MRI imaging modalities as surrogates for tumor cell density iso-surfaces from which a gradient is inferred (Harpold et al. 2007). Treatment simulation results are then directly applicable to the corresponding clinical case. Simulations of the model reveal that the radiotherapy model parameter α is correlated with net proliferation rate λ_c (/year) in such a way that response to radiation, measured in terms of changes to gross tumor volume, can be predicted prior to treatment (Rockne et al. 2008, 2009) in individual patients. The model can be further extended to incorporate resistance factors such as acute or

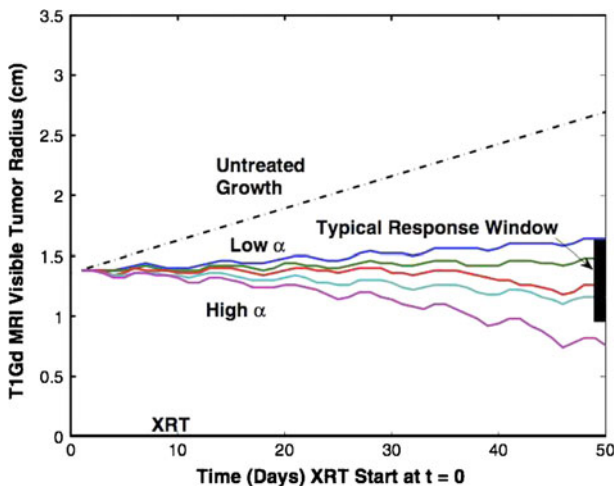


Fig. 3 Simulated tumor growth and response during and after radiotherapy as measured on T1Gd MRI scans for sensitivities of $0.025 \text{ Gy}^{-1} < \alpha < 0.036 \text{ Gy}^{-1}$ compared with the typical response window. Reproduced with permission from Rockne et al. (2009)

chronic oxygen depletion (hypoxia) using an oxygen enhancement ratio (OER) to the α/β ratio in the linear-quadratic model. This OER can be linearly related on a continuous scale to in vivo metrics of hypoxia such as 18F-Fluoromisonidazole positron emission tomography (PET) and applied directly to the radiotherapy simulation of the clinical case. However, the model does not take into account dose-limiting damage to normal tissues, although it can be assumed that tumor response to fractionated radiation differs from normal tissue only as a constant scale factor in the ratio of α/β in the linear-quadratic formulation of biological effect. Furthermore, the model assumes that all cells are equally sensitive and that sensitivity does not vary with cell cycle phase (Pawlik and Keyomarsi 2004).

In another theoretical study a novel treatment strategy for early stage breast cancer is compared to the standard protocol. Enderling and colleagues derived a mathematical model of breast cancer development from healthy tissue and areas with a pre-disposition to develop cancer (Enderling et al. 2006, 2007a, b; Enderling and Vaidya 2008). Once a cancer cell has developed, the spatio-temporal tumor dynamics are described as

$$\frac{\partial c}{\partial t} = \overbrace{\lambda_c c (A_{\max} - A)}^{\text{cell proliferation}} + \overbrace{\phi \nabla^2 c}^{\text{motility}} - \overbrace{\psi \nabla \cdot (c \nabla f)}^{\text{haptotaxis}} - \overbrace{S(x, f, c, \xi_c)}^{\text{surgery}} - \overbrace{R(\alpha, \beta, d, t)c}^{\text{radiotherapy}} \quad (5)$$

where A_{\max} is the host carrying capacity, A is the sum of all cell populations in the domain (healthy tissue, pre-neoplastic lesions and tumor cells), and $S(x, f, c, \xi_c)$ describes surgical removal of cancer cell densities c that are above the tissue density f at position x at the time the tumor has exceeded the detection threshold ξ_c . The tumor development and growth dynamics model is used to compare tumor control with novel single-dose Targeted intra-operative radiotherapy (Targit) (Vaidya et al. 2001, 2002) to the standard course of 5 weeks adjuvant external beam radiotherapy of 50 Gy delivered in 25 fractions. Simulations show that small populations of residual cancer cells after surgical excision are eradicated by both adjuvant radiation protocols (Fig. 4), although the high dose delivered by Targit also sterilizes a portion of the surrounding tumor bed.

Other complex models include individual tumor and normal cell response to and dynamics during fractionated radiotherapy. Ribba et al. (2006) proposed a multiscale model of complex cancer growth including cell cycle regulation and cell cycle phase-dependent radiosensitivity. Here, tumor growth is regulated by hypoxia, the lack of oxygen in the core of a tumor, and by quiescence arising in the tumor core due to spatial constraints. As above, the tumor population is described by an advection equation

$$\frac{\partial c_\varphi}{\partial t} = \overbrace{\lambda_\varphi}^{\text{proliferation}} - \overbrace{\nabla \cdot (vc_\varphi)}^{\text{cell flow in extra-cellular matrix}} \quad (6)$$

$$v = -k \nabla p \quad (7)$$

$$\varphi \in \{G_1, S, G_2, M, G_0, Apop\} \quad (8)$$

where c_φ is the population of cancer cells in cell cycle phase φ , and p is the pressure field of the extra-cellular matrix with permeability k . Oxygen concentration is modeled by a diffusion-consumption equation. Constant maximum oxygen

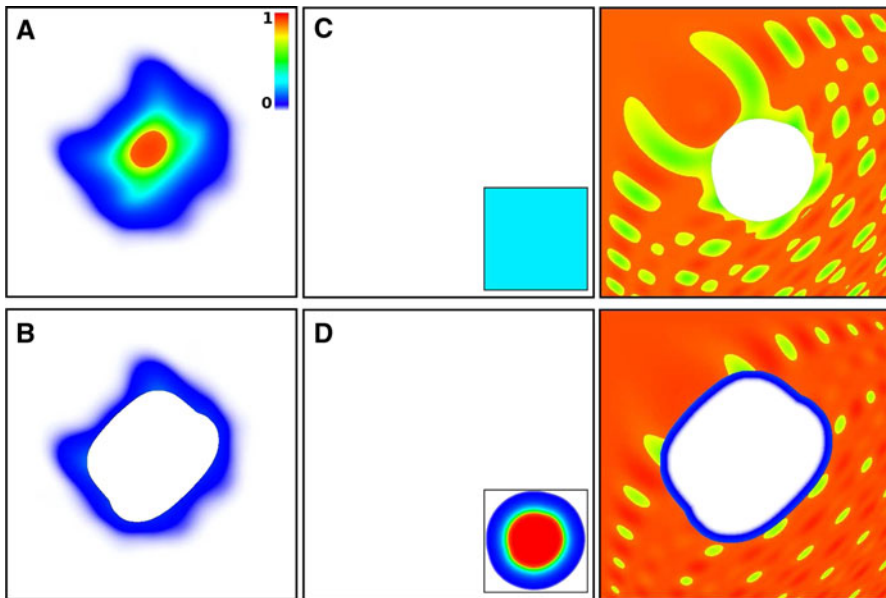


Fig. 4 Simulation of tumor growth, surgery and radiotherapy. **a** Simulated tumor growth after $t = 58$ years. Tumor densities are color-coded. **b** Residual tumor population after surgical excision. **c** Simulation of treatment with standard fractionated radiotherapy (uniform $2 \text{ Gy} \times 25$, *inset*). The tumor is completely eradicated (*left panel*), healthy tissue densities shown in *right panel* (density is color-coded as in *panel A*). **d** Simulation of treatment with Targit (radial dose fall off, *inset*; dose is color-coded with *red*: 20 Gy , *blue*: 0 Gy). The tumor is completely eradicated (*left panel*) as well as the tumor bed (*right panel*). Adapted from Enderling and Vaidya (2008)

concentration is assumed at the spatial position of two blood vessels placed near the center of the domain. If the oxygen concentration falls below a certain threshold, cells experience hypoxia and become growth arrested in G_0 phase. Visualization of the mitotic fraction reveals that the tumor core becomes quiescent due to overpopulation and hypoxia. The cell cycle compartment model enables the inclusion of different radiosensitivities for different cell cycle phases, and simulations predict how a tumor will respond to radiotherapy dependent on cell-cycle specific radiosensitivity (Fig. 5). In summary, the Ribba model (Ribba et al. 2006) shows that tumor geometry, tissue dynamics, and intra-tumoral hypoxia resulting in heterogeneous radiosensitivities are important features that need to be considered when predicting the response of tumors to radiotherapy. Similar results and conclusions are drawn in a different mathematical model of actively proliferating cancer cells and quiescent cells and the transition between both compartments during radiotherapy (Dawson and Hillen 2006).

4 Discrete Tumor Models and Radiation Response

In discrete tumor models, cells are defined as individual agents that reside on a discrete lattice. The behavior of the cells is described by a number of intrinsic

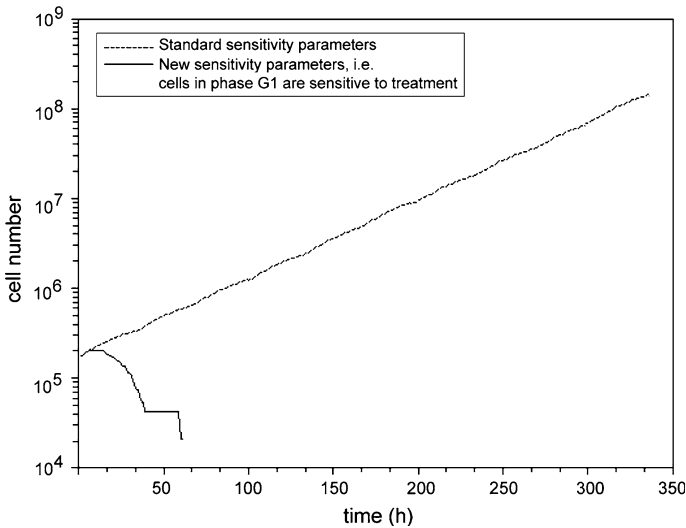


Fig. 5 Different radiotherapy treatment response dependent on cell-cycle specific radiosensitivities. Only if cells in G_1 phase are radiosensitive tumor control can be achieved. Reproduced with permission from Ribba et al. (2006)

parameters and a set of defined rules. From simulations of a small, large, or an evolving number of cells and their interactions with one another as well as their competition for environmental resources, complex population dynamics emerge. A salient feature of these “agent-based” constructs is that the response of individual cells to radiation can be studied, as well as communication between irradiated cells and non-irradiated bystander cells.

Given the newly recognized importance of bystander effects, where one irradiated cell may communicate and confer damage to many unirradiated cells (Hall 2003; Barcellos-Hoff and Costes 2006), such modeling can be particularly advantageous. Richard et al. (2009) developed a cellular automaton model of tumor growth and in vitro response of cells to targeted irradiation. The cells are described by a cell cycle with phase-dependent radiosensitivities, and respond to irradiation by emitting a dose-related signal that can trigger cell death in unirradiated cells nearby. Simulations of irradiation with different doses revealed a non-monotonic survival curve at low doses and monotonic decreases with doses above 0.5 Gy. Furthermore, the model shows a significant contribution of the bystander effect for doses above 1 Gy, but not at low dose radiation such as 0.05 Gy. In vivo, however, most cells are directly hit by radiation at larger doses and thus the bystander effect only contributes to the dynamics on a higher order.

A cellular automaton model that alternatively tracks the fate of cancer stem cells and non-stem cancer cells within a developing tumor was developed by Enderling et al. (2009a, b, c). The cancer stem cell hypothesis motivating this approach is now supported by much evidence and has far-reaching implications for tumor development and targeting (Reya et al. 2001; Dalerba et al. 2007; Rich 2007). With this model, the authors found that, depending on symmetric division frequency

in cancer stem cells, different tumor growth rates as well as cancer stem cell ratios in tumors of comparable sizes would result. Simulations show that the number of cancer stem cells and their division pattern also determine tumor control probability. Tumors can be eradicated if both the stem cell ratio and the symmetric division frequency are low, whereas a tumor cannot be controlled for a large range of other values for the number of stem cells and their repopulation (Fig. 6).

These models are quite adaptable. The governing rules in cellular automaton models can be easily modified as novel biological information becomes available. We show one such adaptation of the above model in which intrinsic cancer stem cell radioresistance is assumed (Bao et al. 2006; Philips et al. 2006; Baumann et al. 2008; Li et al. 2008). Simulations now show that during every boost of radiation cancer stem cells become enriched and increase in number as competing non-stem cancer cells die (Fig. 7). This provides one explanation of the ubiquitous and frustrating clinical “accelerated re-population” (the 2nd “*R*”) (Roberts and Hendry 1993; Withers et al. 1988), in which cell killing is responded to by a more vigorous regrowth of the tumor than occurred originally.

5 Discussion

Mathematical modeling of biological systems has proven to be a useful tool in understanding complex dynamics and identifying the contribution of different mechanisms and parameters in the evolving population. In recent years the number of mathematical models for tumor growth, avascular and vascular, has increased dramatically (Araujo and McElwin 2004; Lowengrub et al. 2009), and a straightforward application of such models has been to simulate treatment response and predict novel strategies (Basse and Ubezio 2007). Although chemotherapy has been simulated extensively through the modeling of tumor-induced vasculature (Liu et al. 2007; Frieboes et al. 2009; Gordon et al. 2009), much less attention has been devoted to formulating and analyzing dynamic models of conventional tumor

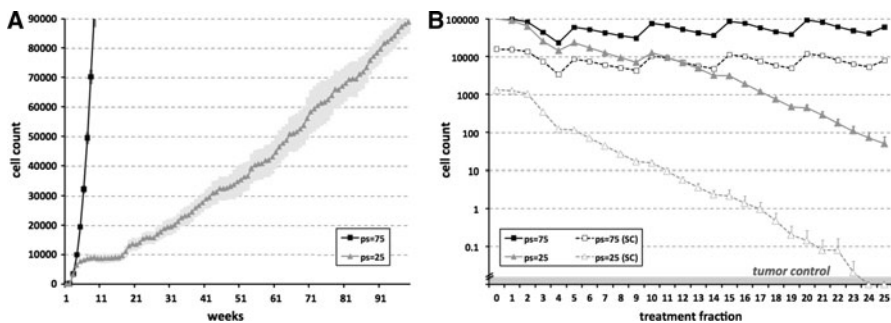
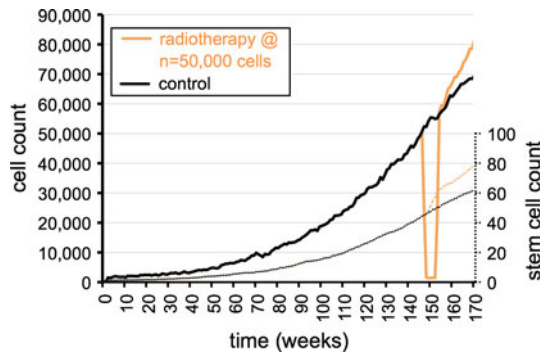


Fig. 6 Simulations of the impact of stem cell ratio and quiescence on radiotherapy success. **a** Simulations of tumor growth for different symmetric stem cell division probabilities p_s (in %). Shown are the averages and standard errors of 10 simulations each. **b** Population dynamics of tumors with different cancer stem cell numbers during $2 \text{ Gy} \times 25$ fractions of radiotherapy. *Solid* plots show total number of cells, *dotted* plots show number of cancer stem cells. Adapted from Enderling et al. (2009a)

Fig. 7 Accelerated repopulation of cancer stem cells and the whole tumor population during and after radiotherapy due to cancer stem cell radioresistance. Shown are the averages of 10 independent simulations each



radiotherapy. In this paper we have presented some promising modeling approaches to simulate the radiation response of cancer cells and whole tumors. All of these models utilize the clinically established linear quadratic model (LQ-model), which rationalizes the observed curvilinear dependence of $\log(\text{survival})$ on radiation dose fraction. The LQ model is based on a principle of single-hit and multi-hit radiation action on DNA. The parameters for the linear and quadratic repair components can be considered separately for different tissues and tumors, offering a realistic rendering for radiotherapeutic application. Using established tumor growth models one can simulate tumor responses to treatment protocols with varying cellular sensitivities, and by comparing the results to clinical data estimate tumor radiosensitivity parameters (Rockne et al. 2009), or vice versa. The results of such modeling can potentially inform the radiation oncologist on how to tailor treatment plans for individual patients. Mathematical models can further be utilized to predict the success or failure of virtual and novel treatment protocols (Jones and Dale 2007; Marcu and Bezak 2009), such as single-dose intraoperative radiotherapy (Enderling et al. 2006, 2007a, b), hyperfractionation (smaller doses delivered more frequently) or hypofractionation (larger doses delivered less frequently) (Dionysiou et al. 2007), or in combination with other treatment strategies such as angiogenic inhibitors (Ergun et al. 2003). Many mathematical tools are available to answer different biological questions, and *in silico* models have proven to be useful in radiotherapy simulation as cell survival is a probabilistic event dependent on the local environment. It can be shown that small tumors that grow near blood vessels exhibit an intratumoral proliferation gradient, attributable to cells in the tumor core being crowded, deprived of blood (i.e. hypoxic) and thus quiescent, and only cells on the periphery of a clone being active (Ribba et al. 2006). The oxygenation and proliferative states of cells are crucial determinants of treatment response, and the spatio-temporal evolution of the proliferative state of cells during the course of treatment can help schedule fractionated treatment more efficiently (Dawson and Hillen 2006). Theoretical models, while aimed initially to be minimalistic, can be extended to include more biological information as it becomes available or deemed necessary. The inclusion of the novel cancer stem cell hypothesis (that only a small subsection of tumor cells live and proliferate forever, with the rest having a finite generational lifetime (Reya et al. 2001)) allows for the simulation of radiation

response of tumors with different stem cell fractions and stem cell proliferation patterns (Enderling et al. 2009a). These simulations can be compared with clinical data on proliferation dynamical responses to different fractionations (Powathil et al. 2007; Basse and Ubezio 2007) and to estimate the size of the stem cell population, and infer its potential response to new treatment scenarios. Most mathematical models are developed in close observation of clinical data, and thus can prove to be vital in augmenting current biological and clinical radiotherapy knowledge. The initial success of the dynamic models encourages the development of future models that address novel biological aspects, emphasize patient specificity (Burnet et al. 2006; Kirkby et al. 2007), or the induction of secondary cancers after radiation (Sachs et al. 2007).

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