Journal of Theoretical Biology 312 (2012) 76–86

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Tumor growth modeling based on cell and tumor lifespans

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HIGHLIGHTS

- ▸ Heterogeneous damages in radiotherapy are explained by a Markov chain.
- ▸ Explained variables are the cell and tumor lifespans.
- ▸ The mean value of the tumor lifespan is approached by a log function.
- ▸ Tumor control probability can be derived from the tumor lifespan.
- ▸ The appropriate treatment planning is deduced from a ROC curve.

ARTICLE INFO

Article history:
Received 23 January 2012
Received in revised form
5 July 2012
Accepted 9 July 2012
Available online 20 July 2012

Keywords:
Markov chain
Cancer cells
Radiotherapy

ABSTRACT

This paper deals with the lifespan modeling of heterogenous tumors treated by radiotherapy. A bi-scale model describing the cell and tumor lifespans by random variables is proposed. First- and second-order moments as well as the cumulative distribution functions and confidence intervals are expressed for the two lifespans with respect to the model parameters. One interesting result is that the mean value of the tumor lifespan can be approached by a logarithmic function of the initial cancer cell number. Moreover, we show that TCP and NTCP, used in radiotherapy to evaluate, optimize and compare treatment plans, can be derived from the tumor lifespan and the surrounding healthy tissue, respectively. Finally, we propose a ROC curve, entitled ECT (Efficiency-Complication Trade-off), suited to the selection by clinicians of the appropriate treatment planning.

1. Introduction

Cancer is a disease that affects millions of people worldwide. One of the common therapies used to treat cancer is external beam radiotherapy. The ionizations induced by radiation cause a variety of possible lesions in cells (Curtis, 1986) and the most harmful damage are the lesions that affect the DNA structure (Wyman and Kanaar, 2006; Hoeijmakers, 2001). Probabilistic modeling is a helpful tool for describing these biological damages. For instance, the tumor control probability (TCP) (Zaider and Minerbo, 2000; Dawson and Hillen, 2006; Gay and Niemierko, 2007) and the normal tissue complication probability (NTCP) (Lyman, 1985; Kallman et al., 1992) are used to characterize and evaluate the radiotherapy treatment planning. Their mathematical expressions can be derived from different stochastic models of the tumor response such as the linear quadratic model (Fowler, 1989; Zaider and Minerbo, 2000), cell population-dynamic models (Sachs et al., 2001), mixed-effects behavioral models (Bastogne, 2010) and cell cycle models (Kirkby et al., 2002). The main drawback of those mathematical representations is their inability to handle biological heterogeneity. There are different types of heterogeneity (Michelson and Leith, 1997) but we have chosen to focus on the tumor damage heterogeneity. A large majority of models suppose that the cell sensitivity to radiation is constant during the treatment and over the entire cell population. Meaning that a surviving cell is thought to be as viable as an unirradiated cell and that all cells are supposed to have the same survival probability. However, evidence suggests that a damaged cell partially loses its ability to resist. As stressed in Gupta et al. (2011) and Durrett et al. (2011), the intratumor heterogeneity of cell phenotypes or damage is of direct clinical

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http://dx.doi.org/10.1016/j.jtbi.2012.07.008

importance. Therefore, the clinical challenge is to define the suited treatment duration for each patient by accounting for variability of the therapeutic response.

In a previous study (Keinj et al., 2011), we proposed a *multinomial* model of tumor response based on a discrete-time Markov chain. This model is derived from the *Target Theory* and assumes that there exists a number of radio-sensitive sites within the cell, called targets. The cell death is finally caused by the deactivation of those targets by radiation particles. We showed in Keinj et al. (2011) that the *multinomial* model is a generalization of typical target models (Chapman, 2007; Pollard et al., 1955), able to account for the heterogeneity of cell damage caused by the treatment. However, like the majority of models used to measure the tumor response to treatment, the *multinomial* model examines the number of surviving cells in the tumor and not the tumor lifespan.

In this paper, we firstly address the stochastic modeling of the tumor lifespan. We start by considering the lifespan of a single cancer cell that behaves as described in Keinj et al. (2011). It is important to emphasize that the cell lifespan is the minimal random number of radiation dose fractions to be applied to kill the cell. We study this random time by calculating its mean, variance and cumulative distribution function. We then assume that a tumor is a group of independent cells. This allows us to define the lifespan of the tumor as the maximum of individual lifespans. In practice, the tumor lifespan is of clinical importance since it corresponds to the minimal number of radiation dose fractions (*i.e.,* treatment duration) to be applied to completely eradicate the tumor. When the initial number n_0 of cancer cells is not too large, we can explicitly calculate the mean, variance and the cumulative distribution function of the tumor lifespan. When n_0 is large, the previous parameters are no longer calculable. However, we show that, under some assumptions, the mean lifespan of the tumor behaves as a logarithmic function of the initial number n_0. The second goal is to show that TCP and NTCP can be completely formulated with respect to the tumor and normal tissue lifespans. These expressions of TCP and NTCP are finally used to propose a ROC curve, called ECT (Efficiency-Complication Trade-off), suited to the determination of the appropriate treatment schedule.

This paper is structured as follows: in Section 2 we give a reminder of the individual cell behavior (cf. Keinj et al., 2011). In Section 3, we study the cancer cell lifespan T as a random variable, determining its mean, variance and confidence intervals and a related set of numerical results is given. We introduce the tumor lifespan L in Section 4, taking the cell proliferation into account and we study theoretically and numerically this random variable. Expressions for TCP and NTCP are given in Section 5. Before concluding, we also propose the ECT diagram.

2. Behavior of a single cell

The main notations used thereafter are presented in Table 1 and $\log(\cdot)$ denotes the natural logarithm function. In Keinj et al. (2011), a multinomial model of tumor growth relying on the target and hit modeling paradigm and based on a discrete-time Markov chain has been proposed. We keep the same modeling assumptions stated in Keinj et al. (2011). Since they play a crucial role in our model, we should briefly recall them:

- a cell has m targets;
- each target may be made inactive after the application of a fraction dose u_0 with a probability q. The relationship between q and u_0 is given in (5);
- the cell death, due to radiation, happens when the m targets are deactivated;
- between two consecutive dose fractions (*i.e.* during 24 h separating two dose fractions in a conventional daily fractionated radiation schedule), if the cell is still alive then an inactive target may repair with a probability r;
- we suppose that cancer cells that compose the tumor all have the same phenotype;
- to reduce complexity of the model, cell cycle positions are not accounted for;
- we assume that there is no delay effect between the radiation dose applied to the mother cell and the damage consequences on daughter cells.

Table 1
Main notations.

Notations	Definition
k	Discrete time related to the kth dose fraction
u_0	Magnitude of each dose fraction
Z_k	Number of deactivated targets in the cell
Π	Transition matrix associated with the Markov chain (Z_k)
$\mathbf{P}$	Matrix associated with treatment effects
$\mathbf{R}$	Matrix associated with cell repair process
m	Number of targets in a cancer cell
q	Probability to deactivate a target in a cancer cell
r	Probability for an inactive target to be reactivated in a cancer cell
T	Cancer cell lifespan
F	Cumulative distribution function of T
I	$1-\theta$ confidence interval of T
n_0	Initial total number of cancer cells in the tumor
L	Lifespan of the tumor
G	Cumulative distribution function of L
J	$1-\theta$ confidence interval of L
$\overline{m}$	Number of targets in a normal cell
$\overline{q}$	Probability to deactivate a target in a normal cell
$\overline{r}$	Probability for an inactive target to be reactivated in a normal cell
$\overline{T}$	Normal cell lifespan
$\overline{F}$	Cumulative distribution function of $\overline{T}$
$\overline{n}_0$	Initial total number of normal cells in the irradiated zone
$\overline{n}$	The complication threshold number of dead normal cells
$L_{\overline{n},\overline{n}_0}$	Lifespan of the normal tissue

Let Z_k be the random variable denoting the number of deactivated targets in the cell at time k, *i.e.* after the kth dose fraction. $k=0$ corresponds to the beginning of treatment. Moreover, we assume that a constant fraction dose (typically $u_0=2$ Gy) is applied every day. We suppose that (Z_k) is a discrete-time Markov chain, *i.e.* the cell state at time $k+1$ only depends on the current state at time k.

2.1. Probability distribution of Z_k

Let Π be the corresponding transition matrix of (Z_k). We briefly define Π, interested readers can refer to Keinj et al. (2011) for details. The dynamics of (Z_k) takes the effects of dose fractions and repair mechanisms into account

$$\Pi = \mathbf{P}\mathbf{R}, \tag{1}$$

where $\mathbf{P}$ models the treatment effects and $\mathbf{R}$ describes repair mechanisms and given as follows:

$$\mathbf{P}(i,j) = \begin{cases} \binom{m-i}{j-i} q^{j-i}(1-q)^{m-j}, & i \le j, \\ 0, & j < i. \end{cases} \tag{2}$$

$$\mathbf{R}(i,j) = \begin{cases} \binom{i}{j} r^{i-j}(1-r)^{j}, & j \le i < m, \\ 0, & i < j. \end{cases} \tag{3}$$

When $i=m$, $\mathbf{R}(m,m)=1$ and $\mathbf{R}(m,j)=0$ for $0 \le j < m$.