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Radiobiological Modeling in Voxel Constructs

RD Stewart and RJ Traub.

Radiation and Health Technology, Pacific Northwest National Laboratory, Richland, WA, 99352, USA.

Abstract. Although great strides have been made towards integrating the anatomical characteristics of specific patients into Monte Carlo dosimetry calculations, efforts to further improve the effectiveness of radiation treatments for cancer are ultimately limited by our ability to predict, for specific patients, the cell-killing effects of temporally and spatially complex irradiation schemes. To better integrate patient- and tumor- specific data into the treatment planning process and provide the research community with the enabling technologies needed to exploit the full potential of radiation therapy, the Pacific Northwest National Laboratory (PNNL) is developing new software to estimate tumor control probabilities (TCPs) using three-dimensional tissue constructs. To illustrate the potential impact on treatment planning of more detailed tumor response modeling, we present the results of several studies characterizing the effects on the TCP of modulating the temporal and spatial distribution of radiation delivered to an idealized tumor with heterogeneous biophysical properties.

Introduction

To exploit the full potential of radiation therapy, treatment designs must consider the so-called four R's (*1*): repair effects, cell-cycle redistribution (or resensitization) effects, reoxygenation effects, and repopulation effects. As illustrated in Figure 1, as the time between radiation "pulses" increases, repair and repopulation effects tend to ***decrease*** cell killing, whereas reoxygenation and cell-cycle redistribution effects tend to ***increase*** cell killing. The effort to design more effective radiation treatments must ultimately consider the interplay between all four of these effects. However, treatment outcome is determined by the compounded cell-killing effects of individual dose fractions, and any temporal or spatial change in the way that a dose fraction is delivered that enhances tumor-cell killing should also increase the cell-killing effects of the entire treatment. In the typical 30 to 60 minute timeframe needed to deliver a dose fraction, damage repair effects will be far more important than reoxygenation, redistribution, and repopulation effects.

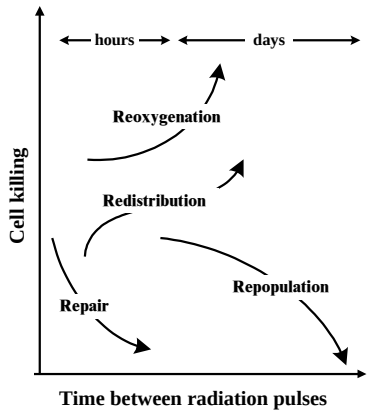

Fig. 1. An idealized schematic illustrating trends in cell killing associated with repair effects, cell-cycle redistribution effects, reoxygenation effects, and repopulation effects. The relative importance of the four effects are not drawn to scale.

Dose fractions are usually delivered using collimators with multiple beam or leaf configurations to shape the radiation field to the contours of the tumor and minimize the dose to surrounding normal tissues. Because irradiator systems cannot be moved instantaneously from one beam or leaf configuration to another, tumor cells experience small pulses of radiation separated by time intervals that range from a few seconds up to a few minutes. Also, cells in different regions of a tumor experience slightly different sequences of radiation pulses because of attenuation and scattering of the radiation beam. Cells are exquisitely sensitive to the size and timing of the radiation pulses they experience, and more realistic, three-dimensional tumor models are needed to better predict the outcome of intensity-modulated radiation therapy (IMRT) treatment designs. To improve tumor response modeling, the Pacific Northwest National Laboratory (PNNL) is developing new software to calculate tumor control probabilities (TCPs) using three-dimensional tissue constructs and an exact description of the series of radiation pulses experienced by tumor cells during the course of a radiation treatment. To illustrate the potential impact on treatment planning of more detailed tumor response modeling, we present the results of several studies characterizing the effects on the TCP of

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modulating the temporal and spatial distribution of radiation delivered to an idealized tumor with heterogeneous biophysical properties.

Methodology

PNNL has developed a computer application called VOXEL, which is based on the Kinetic Biological Effects Modeling (KBEM) software library (http://www.pnl.gov/berc/), to perform TCP calculations using the Lethal and Potentially Lethal (LPL) radiobiological model (*2*) and tabulated dose distributions. In the LPL model, a system of coupled, non-linear ordinary differential equations are used to model DNA damage repair and misrepair processes. The LPL model explicitly accounts for dose and dose-rate effects. Moreover, the widely used linear-quadractic (LQ) formalism (*3*) is a special case of the more general LPL model (*2*). Briefly, the methodology used to compute tumor control probabilities is as follows.

Dosimetry

The MCNP Monte Carlo code (*4*) was used to compute absorbed dose distributions for a cylindrical tissue construct irradiated by broad parallel 1 MeV photon beams from eight different directions as illustrated in Figure 2. Given the tabulated dose distribution for the eight beam directions (labeled A through H in Figure 2), the time required to re-orient the accelerator system (e.g., from configuration A to B), and the time of day when delivery of the dose fraction is initiated, the VOXEL application constructs an absorbed dose rate function, $\dot{D}(t)$, to describe the sequence of radiation pulses experienced by cells in each voxel. The total treatment dose, *D*, is the integral of $\dot{D}(t)$ over all time. The relative intensity of the radiation beams and the beam sequence (e.g., Beam A followed by Beam B followed by Beam C and so on) are user-configurable at runtime. MCNP-calculated dose distributions are re-normalized so that the total treatment dose delivered to a target voxel located near the center of the tissue construct equals a prescribed value, as recommended by the International Commission on Radiation Units and Measurements (*6*).

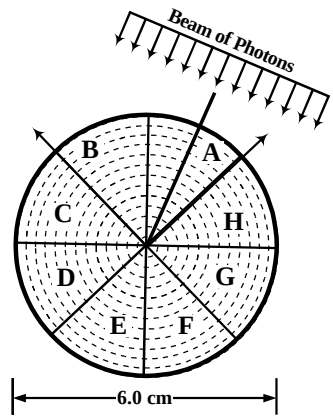

Fig. 2. MCNP geometry and 1 MeV photon beam configurations used for absorbed dose distribution calculations. The tissue construct, a right circular cylinder 6 cm high with a diameter of 6 cm, is composed of soft tissue at a density of 1.04 g cm^{-3} (*5*). For dose tallying purposes, the construct is sub-divided into 2,328 annular voxels as illustrated.

Tumor Control Probability

To estimate the fraction of the initial number of cells that survive in each tissue region, the LPL model is solved by numerical integration, and the probability of tumor control is calculated using the Poisson TCP model (*7*), i.e.,

$$\mathrm{TCP} = \exp\left\{-\sum_{i=1}^{Q} N_i S_i(D)\right\}. \tag{1}$$

Here, *Q* is the number of voxels, N_i is the initial (pre-treatment) number of tumor cells in the *i*th voxel, and $S_i(D)$ is the fraction of the initial number of tumor cells in the *i*th voxel that survive a treatment, as calculated by solving the LPL model with a specific dose rate function $\dot{D}(t)$.

Results

Figure 3 (inset) shows the fraction of irradiated tumor cells that are expected to survive a single dose of low Linear Energy Transfer (LET) radiation delivered at 10 Gy min^{-1}. The cell survival estimates predicted by the LQ model (α=0.22 Gy^{-1} and β=6.47 $\times$ 10^{-2} Gy^{-2}) are within 1 to 5% of the values predicted by the LPL model using three different *biologically plausible* parameter sets: h_{PL} = 2.98 Gy^{-1}

cell^{-1}; h_L = 0.154 Gy^{-1} cell^{-1}; (a) e_{PL} = 1.39 h^{-1}, e_{2PL} = 3.15 × 10^{-2} h^{-1}; (b) e_{PL} = 0.693 h^{-1}, e_{2PL} = 1.57× 10^{-2} h^{-1}; (c) e_{PL} = 0.346 h^{-1}, e_{2PL} = 7.81 × 10^{-2} h^{-1}. That is, the LQ model and the LPL model yield the same "intrinsic radiosensitivity." Although the models predict the same level of cell survival for a single, acute dose of radiation, the TCP calculations shown in Figure 3 clearly demonstrate that cells with the same apparent intrinsic radiosensitivity but slightly different damage repair characteristics (i.e., the e_{PL} and e_{2PL} parameters) respond very differently to the same multi-fraction radiation treatment; the difference is due to damage repair effects. These data highlight the need for detailed modeling of the interplay between damage repair processes and the complex sequence of radiation pulses experienced by cells during the course of a radiation treatment.

For a cylindrical tumor with homogeneous radiosensitivity parameters irradiated by a broad parallel beam of photons, beam sequence most likely has little effect on treatment outcome (*8*). However because of microenvironmental factors (e.g., presence or absence of nutrients or oxygen), genome instability (*9*), and cell signaling phenomena (*10*), cells in different regions of a tumor most likely have very different biophysical (dose-response) characteristics. For a tumor composed of a non-uniform spatial distribution of radioresistant and radiosensitive cells (Figure 4), the results shown in Figure 5 suggest that the sequence of beams used to deliver a dose fraction affects treatment outcome. Moreover, these results suggest that less uniform dose distributions can sometimes produce better treatment outcomes than more uniform dose distributions.

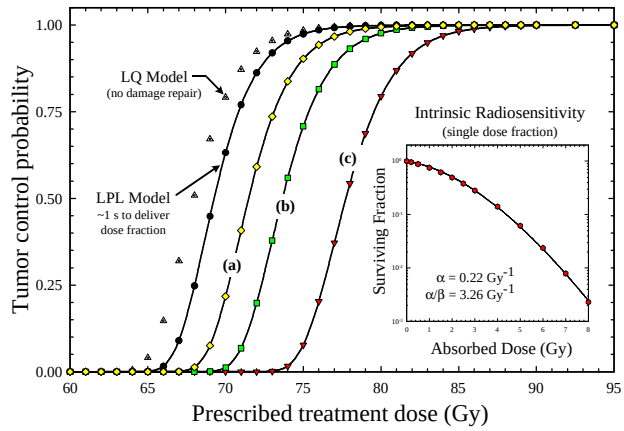

Fig. 3. Effects on TCP of intrinsic cell radiosensitivity. LQ model parameters are for colon adenocarcinoma cells (*11*). TCP calculations are for a uniformly irradiated tumor (30 dose fractions, 1 dose fraction per day) composed of a homogeneous population of 6.9×10^{10} cells. The dose fraction delivery time is 21 minute (8 pulses separated by a 3 minute time interval). LPL model parameters are listed in the main text. Inset figure: (•) LQ model; solid lines LPL model.

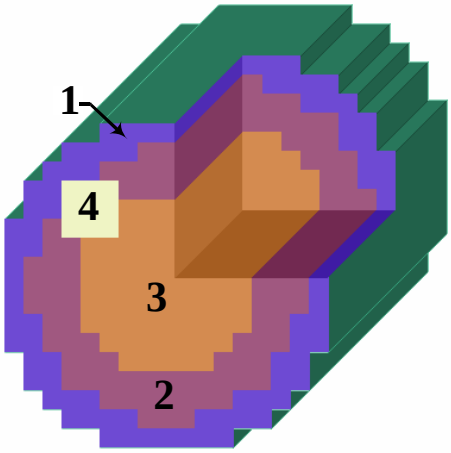

Fig. 4. Cylindrical tumor model with heterogeneous biophysical properties. Tumor parameters are: (1) 10^8 cells cm^{-3} and LPL parameter set (c); (2) 5×10^8 cells cm^{-3} and LPL parameter set (c); (3) 10^8 cells cm^{-3} and LPL parameter set (b); 4) 10^{10} cells cm^{-3} and LPL parameter set (a). For visualization purposes, the cylindrical tumor is sub-divided into 3,133 rectangular voxels and shown with a section cutout. Tissue region 4 is a particularly radioresistant portion of the tumor.

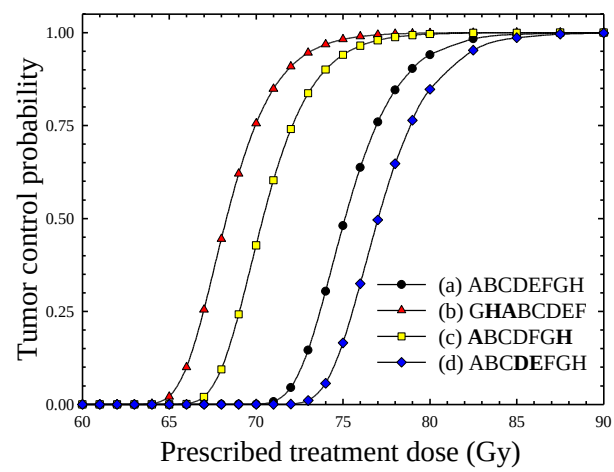

Fig. 5. Effects on the TCP of modulating the beam sequence and beam intensities (30 dose fractions, 1 dose fraction per day, dose fraction delivery time of 28 minutes). (a) uniform beam weights; (b), (c) beams A and H 10 times stronger than the other beams; (d) beams D and E 10 times stronger than the other beams. Curve (b) and (c) are different because of beam sequence effects.

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Conclusions

Results for an idealized tumor with asymmetrical biophysical properties suggest that biological optimization of the way dose fractions are delivered (beam sequence and intensities) could improve some radiation treatments by factors on the order of 5 to 20% (iso-effect dose). The dose distribution that best maximizes the TCP may or may not be a uniform dose distribution. However, when information about the three-dimensional properties of a tumor is not available, the recommended strategy is to deliver a uniform dose of radiation to the planning target volume (*6*) ***as rapidly as possible.*** The compounded effects of delivering the individual dose fractions in a few minutes instead of an hour could improve the effectiveness of some treatments by factors on the order of 1 to 5% (*8*). To fully exploit all four R effects (Figure 1), will, no doubt, require a three-dimensional tumor model that accounts for dynamic changes in the tumor-cell population during the course of the entire treatment. However, static tumor models that capture some of the essential three-dimensional properties of the tumor (e.g., the initial location of hypoxic or rapidly proliferating cells) may prove useful for treatment optimization. With continuing improvements in computer technology and non-invasive imaging techniques, full (all four R) biological optimization of radiation treatments for cancer seems an ambitious but not unreachable goal for the coming decade (*12*). Three-dimensional tumor modeling using software such as our VOXEL application will be needed to unlock the full potential of radiation therapy.

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