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Radiobiological Modeling of Indirect Cell-Kill Mechanisms in Spatially Fractionated Radiation Therapy (SFRT) Treatment of Large and Bulky Unresectable Tumors

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Abstract

Objectives:

Traditional Linear-Quadratic (LQ) model only considers direct cell kill (DCK) mechanisms from either single or multi-track DNA damage. The LQ model has been shown to break down at higher than 10 Gy per fraction as experiments show that the cell survival curve continually bends to the left at higher and higher doses per fraction. Spatially fractionated radiotherapy (SFRT) treatments are typically delivered as a single high dose of 15–20 Gy with a highly heterogeneous dose distribution inside the bulky tumor and as expected, LQ model cannot accurately predict the cell survival for these types of treatments. Additionally, there is no tools or methods developed for physicians to evaluate the biological response of SFRT treatments, yet. Herein we propose a potential for a new cell survival model that considers indirect cell kill (ICK) that may explain the continuous bending of the cell survival curve seen in cell line experiments. By having a mathematical formula that more accurately predicts and models DCK and ICK, the clinical medical physicists and attending physicians may leverage this novel model to enhance the therapeutic ratio of SFRT treatments in conjunction with combination therapy. This will further aid in the improvements of treatments to patients by providing better pain relief and providing higher tumor cell kill for better tumor local control rate. The three ICK mechanisms we included in our new equation is 1) radiation-induced bystander signaling, 2) anti-tumor immune response via release of effector cells, and 3) intratumor microvasculature damage due to SFRT. We developed an early stage, novel spatial voxelized mathematical formula to account the effect of ICK mechanisms in conjunction with the standard LQ model for the highly heterogenous sieve-like and unconventional SFRT dose patterns for large and bulky (⩾ 8 cm) unresectable tumor masses.

Methods:

The traditional LQ model only includes DCK mechanisms, we incorporated three additional factors that considers ICK mechanisms. These three ICK mechanisms are: radiation induced bystander effect, anti-tumor immune response; and microvasculature damage as mentioned above. After development of this new model, we simulated cell survival curves and tumor control probability (TCP) curves based on clinical SFRT dose distributions used in our clinic. Calculations of the cell survival curves are done voxel by voxel in the planning CT data, in order to retain spatial information that is extremely important for the highly heterogenous dose distributions characteristic of SFRT treatments. This model was tuned based on limited clinical patient's outcome data. So far, five patient's clinical outcome data was used. The cohort were head and neck cancer patients (squamous cell carcinoma), treated with SFRT (15 Gy in 1 fraction) via 3D-conformal MLC-based crossfire method with 6MV beam followed by full course of conventional radiation therapy (70 Gy in 35 fractions) via highly conformal VMAT plan. Our revised LQ model still retained the clinical alpha-beta ratio of 10 Gy (for tumor) to model the DCK mechanisms.

Results:

This novel equation modeled ICK mechanisms included 3 ways. Radiation-induced bystander signaling was modeled via Fick's law of diffusion, anti-tumor immune response was modeled by relating fraction of the tumor killed from DCK mechanisms, and microvascular damage was modeled to only take effect at doses >10 Gy. Our simulations study demonstrated that at higher doses (>10 Gy per fraction), our new equation has the cell survival curve continuously bends to the left which wasn't previously seen in traditional LQ model. Additionally, our new cell survival model coincides with the traditional LQ model at lower doses (< 6 Gy per fraction). We aimed to have our new equation be able to describe both high doses fraction and traditional dally fractionated doses. By incorporating ICK mechanisms, we see a shift in the TCP curves to the left.

Without including ICK mechanisms, we get a predicted TCP of 80.0% ± 5.4%, with ICK mechanisms our model gave TCP of 98.3% ± 2.4% for this patient cohort. This suggests that ICK mechanism(s) are a significant contributor to the clinical debulking of large tumors seen with SFRT treatments in our clinical follow up results.

Conclusion(s):

Herein we present a new mathematical formula that adds ICK mechanisms to the traditional standard LQ model to accurately model the cell survival that could correctly predict the TCP for highly heterogeneous, high dose SFRT treatments in conjunction with combination therapy. Having a more accurate prediction of the tumor cell kill (via both DCK and ICK mechanisms) for these SFRT treatments will be highly advantageous for treating radiation oncology physicians to prescribe and evaluate these complex and difficult treatment plans. Furthermore, it will help assist in finding optimal ways to generate a SFRT treatment plan for these heterogenous dose distributions to enhance the ICK. As of now, our model hasn't been tuned for any specific tumor type(s) yet, further work will be done to be clinically deployable for a variety of treatment sites and tumor histologies. Further research will be the validation and tuning of our new proposed radiobiological model, this will be done either through Monte Carlo simulations, human cancer cell line experiments on LINAC, or through a larger patient cohort clinical follow up study.