Radiobiological Modeling of Indirect Cell-Kill Mechanisms and the Linear-Quadratic Model in Spatially Fractionated Radiation Therapy of Large & Bulky Unresectable Tumors

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INTRODUCTION

- The traditional Linear-Quadratic (LQ) model only considers direct cell kill (DCK) mechanisms from either single or multi-track. It has been experimentally shown that LQ model starts to break down at higher than 10 Gy/fraction, the cell survival curve continually bends at higher dose per fraction.[1]
- SFRT treatments are typically delivered as a single dose of 15-20 Gy with a highly heterogeneous dose distribution, as it is hypothesized to induce indirect cell kill (ICK).
- As expected, current LQ model doesn't accurately predict the cell survival for these types of treatments.
- The three main ICK mechanisms responsible for SFRT effectiveness is: (1) radiation-induced bystander signaling, (2) anti-tumor immune response via release of effector cells and (3) microvasculature damage due to highly heterogenous SFRT dose distributions.

AIM

- Traditional Linear-Quadratic (LQ) model only accounts for direct-cell-kill (DCK) mechanisms which underestimates clinical outcomes of spatially fractionated radiotherapy (SFRT).
- We propose a novel equation to account for indirect-cell-kill (ICK) mechanisms in highly heterogenous SFRT dose distributions for large and bulky (≥ 8 cm) unresectable tumors.

METHODS

- We incorporated three additional factors accounting for ICK mechanisms: radiation-induced bystander signaling, anti-tumor immune response, and microvasculature damage.
- Simulations of the new models were performed, plotting cell survival curves and tumor control probability (TCP) curves based on clinical SFRT dose distributions for head and neck (HN) cancer patients.
- Indirect cell kill factors were tuned based on limited clinical outcome data (5 HN cases) obtained. For direct cell kill mechanisms, the clinical α/β of 10 Gy was used.

RESULTS

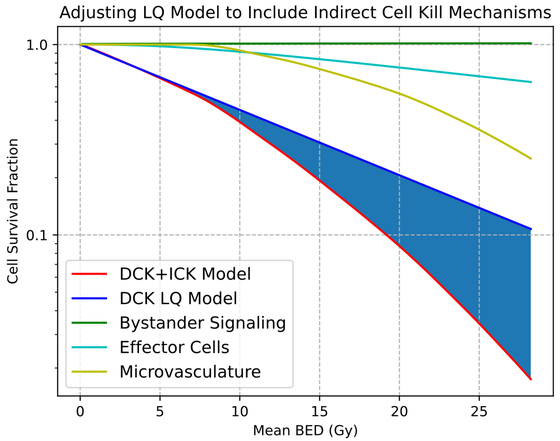

***Fig.1**. Comparison of traditional LQ model and our new proposed model (DCK+ICK). Shaded areas depict contributions from ICK mechanisms as described above. Included are individual contributions from each of the 3 ICK mechanisms*

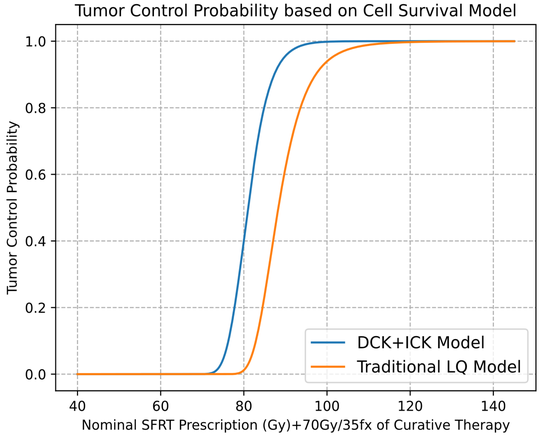

***Fig.2**. Depicts the TCP curves associated with combination therapy (70 Gy/35fx for bulky head and neck tumor)– suggesting new model pushes the TCP curve to the left with higher therapeutic ratio.*

Figure 1 depicts how our new model is compared to the traditional LQ model based on dose distributions shown in **Figure 3.** As shown, our model shows continuous bending at higher doses but also shows convergence to the traditional LQ model at lower doses. Ideally, the new equation should be able to describe both high doses and traditional doses. Radiation-induced bystander signaling was modeled via Fick's law of diffusion; anti-tumor immune response was modeled by relating fraction killed from DCK mechanisms, and microvascular damage was modeled to only take effect at dose greater than 10 Gy per fraction. **Figure 2** demonstrates the effects of our new model on the tumor control probability (TCP) curves. As shown here, the TCP curve is shifted to the left, highlighting that ICK effects may explain why we see clinical debulking properties with longitudinal mass reduction on bulky tumors as a function of SFRT treatment with combination therapy.

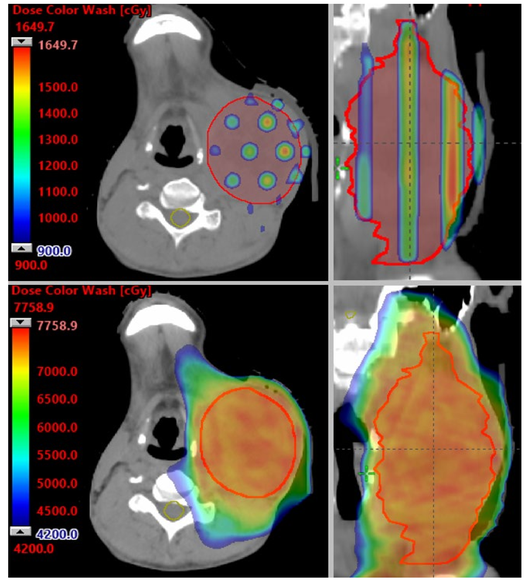

***Fig.3**. Display of SFRT (15 Gy/1fx) and follow-up therapeutic combination therapy (70Gy/35fx) dose distribution in axial (left) and coronal (right) viewing planes for this head and neck patient. Plan was used to help tune new cell survival model. Patient showed a tumor volume reduction of 75% from 6-month follow-up.*

CONCLUSIONS

- Herein we presented a new formalism that incorporates the ICK mechanisms to the traditional LQ equation to model and cell survival curve more accurately for sieve-like dose distributions from SFRT treatments. Having a more accurate prediction of the tumor cell kill for these SFRT plans will be highly advantageous for physicians to prescribe and evaluate entire treatment course.
- As of now, our model has only been roughly tuned with 5 HN cases. Further validating and tuning of our new proposed model for more tumor types will be done either through Monte Carlo simulations, cell line experiments, or through clinical data available in our clinic.

REFERENCES

1. Kirkpatrick JP, Meyer JJ, Marks LB. The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery. Seminars in Radiation Oncology. 2008;18(4):240-243. doi:10.1016/j.semradonc.2008.04.005

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