Linear-Quadratic Model and Beyond, For Combined Therapies Against Brain Cancers

Sara Strom; Shannon Van Ginkel, Anne Hubbard, Dr. Andrew Ekpenyong
Department of Physics, Creighton University, Omaha, NE, USA

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ABSTRACT

Purpose: Glioblastoma (GBM) remains a lethal brain cancer with a devastating median survival of about 15 months with the current standard of treatment involving surgery, radiation therapy, and chemotherapy utilizing temozolomide (TMZ). Radioimmunotherapy (RIT), combining RT with immunomodulatory agents like lenalidomide, as well as nanoparticle mediated radiotherapy are promising combination modalities. Accurate biophysical modeling of cell survival from *in vitro* assays is critical for optimizing such combined therapies. The Linear-Quadratic (LQ) model is the standard for interpreting clonogenic survival data following RT. This work investigates the application and limitations of the LQ model for characterizing the effects of single-agent and combined lenalidomide-RT treatments in GBM cell lines.

Methods: Clonogenic survival assays were performed on human GBM cell lines U87 and T98G treated with RT alone (0-50 Gy, Faxitron CellRad), lenalidomide alone, and their combination, as well as NPRT. Survival curves were fitted with LQ models. N2A cells were used as non-GBM controls.

Results: Interestingly, many of the survival curves had up to 6 decades on the survival fraction axis, leading to significant deviation of alpha/beta parameters from expected values for the literature. Classic explanation for such deviations exist: LQ model fails beyond about 3 decades of cell killing because the model's quadratic component causes it to over-predict the lethality of large radiation doses. We will present both the LQ model results and alternative models such as the universal survival curve model.

Conclusion: Our work demonstrates a noted limitation of the LQ model and provides impetus for exploration of complementary/alternative radiobiological models to better capture experimental results.

CONTACT

Dr. Andrew Ekpenyong
Creighton University
AndrewEkpenyong@Creighton.edu

BACKGROUND

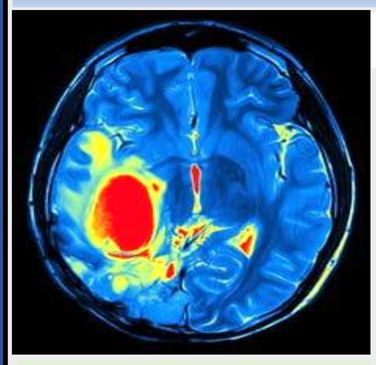


Figure 1. MRI shows a GBM tumor located in the posterior left temporal lobe.

Figure 2. Radiation therapy using mask-based Gamma Knife. Commonly used but largely ineffective in the long-term mitigation of GBM.

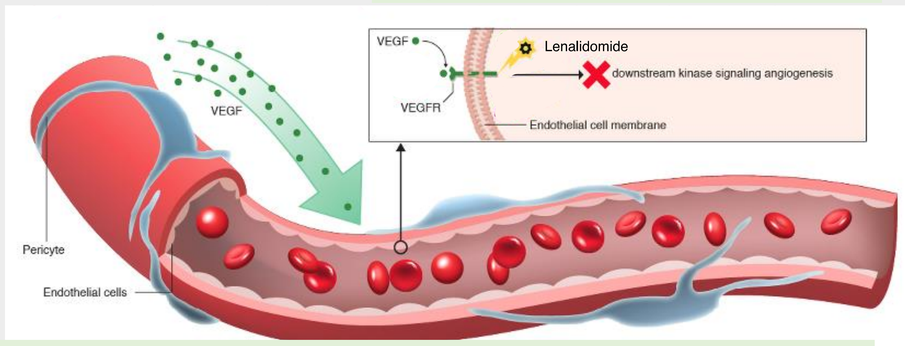


Figure 3. Lenalidomide as an Angiogenesis Inhibitor. By blocking the VEGF signaling cascade, Lenalidomide inhibits the development of new blood vessels, crucial for tumor growth and metastasis.

MATERIALS AND METHODS

The experimental setup includes a Faxitron CellRad cell irradiator and Electric Cell Impedance Sensor (ECIS). This allows for the quantification of cell migration after the application of both radiotherapy and chemotherapy with lenalidomide. The CytoSMART Omni imaging system and clonogenic assay plates monitor colony formation following treatment to determine cell survival and reproductive integrity after combined therapy.

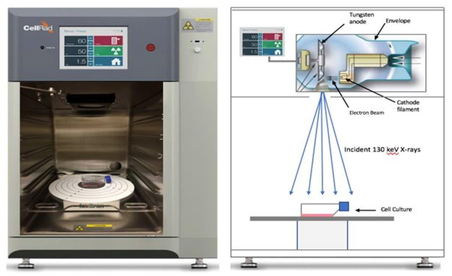
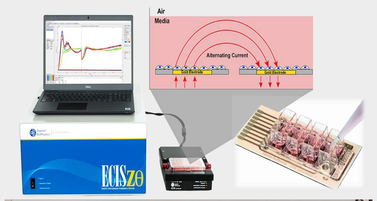


Figure 5. Faxitron CellRad (Above) Irradiates cells in doses ranging from 2 - 50 Gys.

Figure 4. Electronic Cell Impedance Sensing (ECIS) (Below) examines and quantifies real time cell migration at the 2D level. Results expected in 7 days.



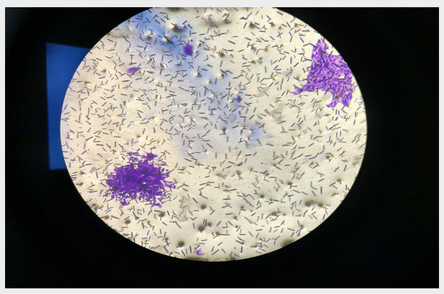


Figure 6. (Above) CytoSMART Omni is used to perform clonogenic assays.
Figure 7. (Left) Clonogenic Assay Hand-Count Method of T98G cell colonies under 20x magnification

Analysis and LQM Curve Fitting

$$PE = \frac{number\ of\ colonies\ formed}{number\ of\ cells\ seeded}$$

Equation 1. Plate Efficiency

$$SF = \frac{number\ of\ colonies\ formed}{(number\ of\ cells\ seeded) \times (PE)}$$

Equation 2. Survival Fraction

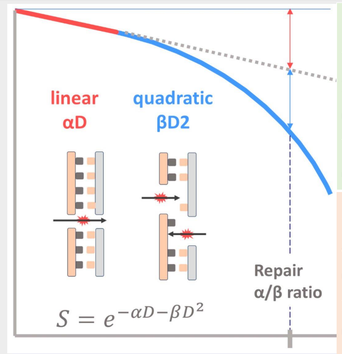
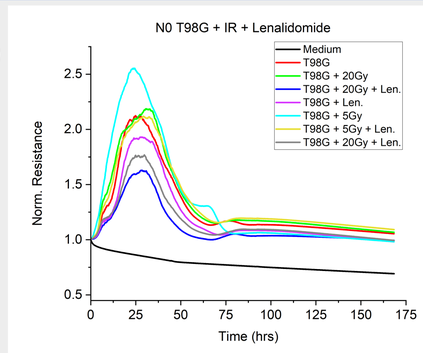


Figure 8. LQM Fitting of Survival Data. Cell survival was modeled using the Linear Quadratic Model: $S(D) = e^{-(\alpha D + \beta D^2)}$ where S = surviving fraction, D = radiation dose, α and β = fitting parameters for linear and quadratic components of cell killing, respectively. Nonlinear regression was used to derive α/β values, which quantify radiosensitivity and the dose-dependent effect of lenalidomide.

Beyond LQM. The Quadratic-Cubic Linear (QCL) model extends the LQM: $S(D) = e^{-(\alpha D + \beta D^2 + \gamma D^3)}$ The cubic term γ captures increased cell kill at high doses or complex bystander effects, offering enhanced flexibility for modeling tumor responses for combined therapies. The Universal Survival Curve (USC) is another candidate model beyond LQM.

RESULTS

a)



b)

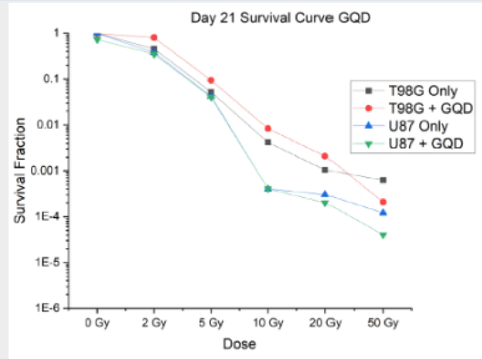
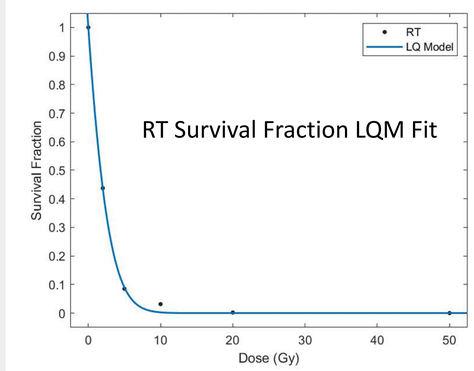
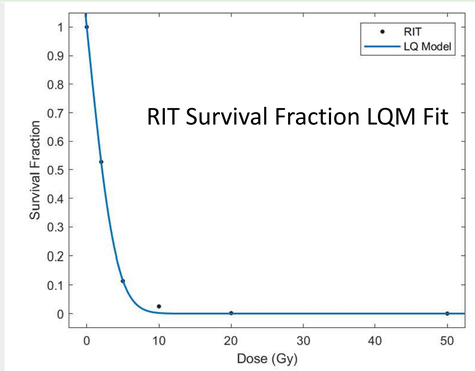


Figure 9. (a) ECIS Migration of T98G treated with radiation and Lenalidomide **(b)** Survival Curves for T98G + GQD at day 21. Note 6 decades of cell killing. The LQM did not produce expected α/β values.





	α value average (Gy^{-1})	β value average (Gy^{-2})	α/β ratio (Gy)
N2A + RT	0.3695 ± 0.0971	0.0227 ± 0.0335	16.2775 ± 2.8985
N2A + RIT	0.2468 ± 0.0622	0.0368±0.0209	6.7065±2.9761

Table 1. LQ model parameters α, β, and α/β ratio for N2A cells under RT alone and RIT

DISCUSSION AND CONCLUSIONS

- LQ model is inadequate for accurately modeling the clonogenic survival of GBM cell lines T98G and U87, as well as the control N2A neuroblastoma cells at the high, ablative radiation doses (>15 Gy) relevant to emerging radioimmunotherapy (RIT) protocols.
- The Universal Survival Curve (USC) model offers a significantly improved biophysical framework, accurately capturing both the low-dose shoulder and the high-dose linear tail of the survival curve.
- Using the USC model, we confirm that a measurable fraction of N2A cells survives high-dose RT, supporting the clinical strategy of combining RT with lenalidomide to target these residual, therapy-resistant cells.
- Ongoing/Future Work: We will apply the USC model to our U87 and T98G GBM datasets to quantify the radiosensitizing effects of lenalidomide and nanoparticle-mediated radiotherapy (NPRT) with greater accuracy, aiming to optimize fractionation schedules for brain cancer patients.

ACKNOWLEDGEMENTS

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