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Estimation of transition doses for human glioblastoma, neuroblastoma and prostate cell lines using the linear-quadratic formalism

John Akudugu, Antonio Serafin

Division of Radiobiology, Department of Medical Imaging and Clinical Oncology, Stellenbosch University, Cape Town, South Africa

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Original Article

Abstract

Purpose: The introduction of stereotactic radiotherapy has raised concerns regarding the use of the linear-quadratic (LQ) model for predicting radiation response for large fractional doses. To partly address this issue, a transition dose D^* below which the LQ model retains its predictive strength has been proposed. Estimates of D^* which depends on the α, β, and D_0 parameters are much lower than fractional doses typically encountered in stereotactic radiotherapy. D_0, often referred to as the final slope of the cell survival curve, is thought to be constant. *In vitro* cell survival curves generally extend over the first few logs of cell killing, where D_0-values derived from the multi-target formalism may be overestimated and can lead to low transition doses. **Methods:** D_0-values were calculated from first principles for each decade of cell killing, using experimentally-determined α and β parameters for 17 human glioblastoma, neuroblastoma, and prostate cell lines, and corresponding transition doses were derived. **Results:** D_0 was found to decrease exponentially with cell killing. Using D_0-values at cell surviving fractions of the order of 10^{-10} yielded transition doses ~3-fold higher than those obtained from D_0-values obtained from conventional approaches. D^* was found to increase from 7.84 ± 0.56, 8.91 ± 1.20, and 6.55 ± 0.91 Gy to 26.84 ± 2.83, 23.95 ± 2.03, and 22.49 ± 2.31 Gy for the glioblastoma, neuroblastoma, and prostate cell lines, respectively. **Conclusion:** These findings suggest that the linear-quadratic formalism might be valid for estimating the effect of stereotactic radiotherapy with fractional doses in excess of 20 Gy.

Keywords: Transition Dose; Linear-Quadratic Model; Stereotactic Radiotherapy

Introduction

The α and β parameters of the linear-quadratic (LQ) model are routinely used to estimate the biologically effective dose (BED) which has long been very valuable in making comparisons between the effects of different dose-fractionation schemes.[1-6] Following the introduction of stereotactic and hypofractionated radiotherapy over two decades ago, researchers have questioned the appropriateness of using the LQ model to predict treatment outcome, especially when large fractional doses are administered.[7-12] The LQ model has been the preferred algorithm for evaluating the effects of radiotherapy with doses per fraction ≤ 10 Gy for decades, but with the advent of stereotactic radiotherapy it has been suggested that the model may not be valid when doses exceeding 15 Gy are acutely delivered.[13] The overriding reason for this concern is that it predicts much higher levels of cell kill than those observed in the clinic and *in vivo* systems.[7] Using both single-cell and spheroid cultures, Iwata *et al.* have shown that the use of the LQ model to convert doses of hypofractionation schedules to single doses can result in significant underestimation of the potency of hypofractionated radiation treatment.[11] A similar conclusion was reached by these investigators in studies on a murine tumor model.[14] Notably, these investigations demonstrated that BED values calculated using the LQ formalism can be as low as 30% of those that are actually measured. More recently, Iwata *et al.* compared the LQ model with the repairable-conditionally-repairable and multi-target models and concluded that the former should not be used for high dose per fraction radiotherapy for similar reasons.[15] However, the predictive capacity of the LQ formalism appears to be dependent on tissue and tumor type; and it has been suggested that for certain tissues, use of the LQ model to evaluate hypofractionated and stereotactic radiotherapy may be valid for fractional doses of the order of 18 - 20 Gy.[4,16] The LQ formalism has been successfully used in the clinic for the evaluation of biologically effective doses for tumor control and normal tissue complication for fractional doses of 5 - 27 Gy.[17-20] Clearly, there is controversy regarding the clinical application of the LQ formalism when single or a few large fractional doses of radiation are used.[9-12]

Corresponding author: John Akudugu; Division of Radiobiology, Department of Medical Imaging and Clinical Oncology, Stellenbosch University, Cape Town, South Africa

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Given that fractional doses exceeding 15 Gy may be used in stereotactic radiotherapy[21-24], there has been a recent increase in the desire to re-evaluate the applicability of the LQ model in radiotherapy regimens employing large doses per fraction. To address potential shortcomings of the LQ model in its utility in stereotactic and hypofractionated radiotherapy, some investigators have suggested modifications to the LQ model for high fraction doses.[7, 10, 13, 25, 26] Although these extensions to the LQ model seem to have improved capacity to fit experimental data at high doses, Fowler cautioned researchers not to totally abandon the model on the grounds of its failure to predict radiosensitivity at high levels of cell kill.[27]

One cell survival parameter that has not enjoyed the same level of popularity as the α and β coefficients in predicting clinical outcome is D_0 which is an indicator of the behavior of cell survival curves at high acute radiation doses. Recently, the importance of D_0 in estimating the dose at which the LQ model starts to depart from the modified LQ (MLQ) model as proposed by Guerrero and Li was highlighted.[7, 10] The MLQ model uses the well-defined α and β parameters and retains the simplicity of the LQ model.[7] Also, the MLQ model introduces a shift parameter, δ, in the dose protraction factor from which the dose, D^*, at which the LQ model begins to deviate from mechanism-based models like the lethal-potential lethal model can be derived.[7] In addition to α and β, δ depends on D_0. The latter is often referred to as the reciprocal of the final slope of the cell survival curve, and should be a cell-type specific constant at high doses. Determination of D_0 from *in vitro* cell survival data, using either the LQ or the multi-target model, has typically been possible over the first 3 logs of cell kill giving D_0 values of 1.0 – 3.7 Gy.[1, 28-35] It is conceivable that values of D_0 derived at higher levels of cell kill may differ markedly from those obtained in the first few logs of cell kill, and can have a significant impact on the magnitude of the δ-parameter. Hence, the role of D_0 in determining the appropriateness of the LQ formalism in modeling radiation response in stereotactic radiotherapy needs further evaluation.

In the following, data for 17 cancer cell lines spanning a wide range of radiosensitivities [36-38], were used to test whether D_0, as originally defined, is indeed independent of the level of cell kill. The implications of a potential dependence of D_0 on the extent of cell kill on the strength of the LQ model as a predictor of radiosensitivity at high radiation absorbed doses are further discussed.

Methods and Materials

Estimation of D_0 from the multi-target model

From the multi-target formalism and for sufficiently large radiation absorbed doses, the cell surviving fraction, S_D, is related to radiation absorbed dose, D, by:

$$-ln(S_D) = (1/D_0)D + k \qquad (1)$$

where, k is a cell type-dependent constant. D_0-values were derived from the slope of a linear regression fit according to Equation (1) for $S_D \leq 0.1$ and absorbed doses not greater than 10 Gy, using cell survival data for 17 cell lines from three different cancer types [36-38], and were subsequently used to calculate transition doses for comparison with those determined from the LQ formalism.

Derivation of D_0 and transition dose from LQ model

According to the linear-quadratic model, the surviving fraction S_D of a population of cells exposed to an absorbed radiation dose, D, is given by the equation:

$$S_D = e^{-(\alpha D+\beta D^2)} \qquad (2)$$

where, α and β are the coefficients of the linear and quadratic components of cell killing, respectively. Equation (2) may be rearranged as a quadratic function of the form:

$$\beta D^2 + \alpha D + lnS_D = 0 \qquad (3)$$

Solving Equation (3), the absorbed dose corresponding to a surviving fraction of S_D is given by:

$$D_{S_D} = \frac{-\alpha + \sqrt{\alpha^2 - 4\beta(lnS_D)}}{2\beta} \qquad (4)$$

By definition, the D_0 is the dose required to decrease the surviving fraction from 1.0 to 0.37, 0.1 to 0.037, 0.01 to 0.0037, and so on.[39] Therefore, D_0 may be calculated from the doses determined in Equation (4) as follows:

$$D_0 = \begin{cases} D_{0.37} - D_{1.0}, for\ the\ 1^{st}\ log\ of\ cell\ killing \\ D_{0.037} - D_{0.1}, for\ the\ 2^{nd}\ log\ of\ cell\ killing \\ D_{0.0037} - D_{0.01}, for\ the\ 3^{rd}\ log\ of\ cell\ killing \end{cases} \qquad (5)$$

Similarly, D_0 can be calculated for up to 10 or more logs of cell killing as may be required to ensure control of a tumor containing < 10^{10} malignant cells.[30] D_0 is often referred to as the "final slope" of the cell survival curve, and is thought to be constant when derived beyond the "shoulder" of the curve regardless of the log of cell killing. To interrogate this notion, the relationship between D_0 and the level of cell killing was evaluated for 17 human cell lines of different origins (**Table 1**). In this study, data for 6 glioblastoma, 4 neuroblastoma, and 7 prostate cell lines were used.[36-38] Experimentally determined α and β coefficients were used to calculate D_0, as described in Equations (4) and (5). For each cell line, α and β were derived from 6 - 7 cell survival data points within the absorbed dose range of 0 – 10 Gy. The obtained D_0-values were then plotted against the n^{th} log of cell killing, and fitted to a two-phase exponential decay function of the form:

$$D_0 = ae^{-k_1 n} + be^{-k_2 n} + c \qquad (6)$$

where a, b and c are cell line-specific constants, and D_0 decays with rate constants k_1 and k_2. The dose protraction shift parameter, δ, can be determined from D_0, as follows[7]:

$$\delta = \frac{2\beta D_0}{1-\alpha D_0} \qquad (7)$$

from which the transition dose D^* can be derived as the reciprocal of δ.[7]

TABLE 1: Summary of parameters derived from the multi-target and linear-quadratic models for seventeen human cell lines.

			Multi-target model			Linear-quadratic model		
Cell line	**α (Gy^{-1})$^{\#}$**	**β (Gy^{-2})$^{\#}$**	***D*o (Gy)§**	**δ (Gy^{-1})§**	***D*** (Gy)§**	***D*o (Gy)§**	**δ (Gy^{-1})§**	***D*** (Gy)§**
Glioblastoma[36,37]								
G44	0.17±0.03	0.03±0.00	1.61±0.27	0.133±0.040	7.52±2.24	0.64±0.03	0.043±0.004	23.25±1.87
G112	0.21±0.03	0.01±0.00	2.41±0.22	0.098±0.032	10.25±3.39	0.99±0.05	0.025±0.003	40.19±4.04
G120	0.18±0.03	0.04±0.00	1.21±0.02	0.124±0.007	8.08±0.42	0.55±0.03	0.049±0.004	20.36±1.60
G62	0.20±0.05	0.03±0.01	1.54±0.06	0.134±0.067	7.49±3.75	0.59±0.03	0.040±0.006	25.15±3.54
G28	0.15±0.01	0.02±0.00	2.55±0.01	0.165±0.008	6.05±0.29	0.87±0.05	0.040±0.003	24.95±1.74
G60	0.37±0.09	0.02±0.01	1.48±0.09	0.131±0.078	7.64±4.53	0.69±0.03	0.037±0.005	27.17±3.84
	Mean±SEM		1.80±0.22	0.131±0.009	7.84±0.56	0.72±0.07	0.039±0.003	26.84±2.83
	CV		30.32%			23.86%		
Neuroblastoma[36]								
SK-N-BE(2c)	0.24±0.03	0.03±0.01	1.22±0.07	0.104±0.014	9.66±1.27	0.58±0.03	0.041±0.007	24.66±4.08
SK-N-SH	0.66±0.11	0.02±0.01	0.99±0.02	0.114±0.036	8.76±2.72	0.64±0.02	0.045±0.008	22.32±3.83
KELLY	0.77±0.14	0.01±0.01	1.00±0.08	0.087±0.037	11.49±4.84	0.74±0.01	0.034±0.005	29.19±3.92
SHSY5Y	0.54±0.07	0.02±0.01	1.30±0.15	0.175±0.054	5.73±1.79	0.76±0.02	0.051±0.007	19.61±2.85
	Mean±SEM		1.13±0.08	0.120±0.019	8.91±1.20	0.68±0.04	0.043±0.004	23.95±2.03
	CV		13.88%			12.04%		
Prostate[37,38]								
0.27±0.02	0.27±0.02	0.02±0.00	1.71±0.09	0.127±0.037	7.87±2.30	0.73±0.04	0.036±0.003	27.63±2.14
0.29±0.05	0.29±0.05	0.02±0.01	1.50±0.07	0.106±0.035	9.42±3.13	0.80±0.04	0.042±0.006	23.95±3.27
0.38±0.07	0.38±0.07	0.02±0.01	1.47±0.12	0.133±0.039	7.51±2.19	0.73±0.03	0.040±0.006	24.73±3.85
0.49±0.03	0.49±0.03	0.01±0.00	1.73±0.09	0.227±0.066	4.40±1.27	0.95±0.02	0.036±0.003	28.01±2.67
0.61±0.02	0.61±0.02	0.01±0.00	1.31±0.02	0.130±0.073	7.69±4.28	0.90±0.01	0.040±0.003	25.07±1.95
0.63±0.04	0.63±0.04	0.01±0.01	1.48±0.04	0.438±0.192	2.28±1.00	1.15±0.02	0.085±0.009	11.73±1.28
0.24±0.05	0.24±0.05	0.06±0.01	0.96±0.07	0.150±0.049	6.68±2.16	0.46±0.02	0.061±0.003	16.31±1.68
	Mean±SEM		1.45±0.10	0.187±0.044	6.55±0.91	0.81±0.08	0.049±0.007	22.49±2.31
	CV		18.00%			26.76%		

$^{\#}$ Errors were derived from data fitted to LQ model; β-errors less than 0.005 were set to zero; §errors were calculated using appropriate error propagation formulae.

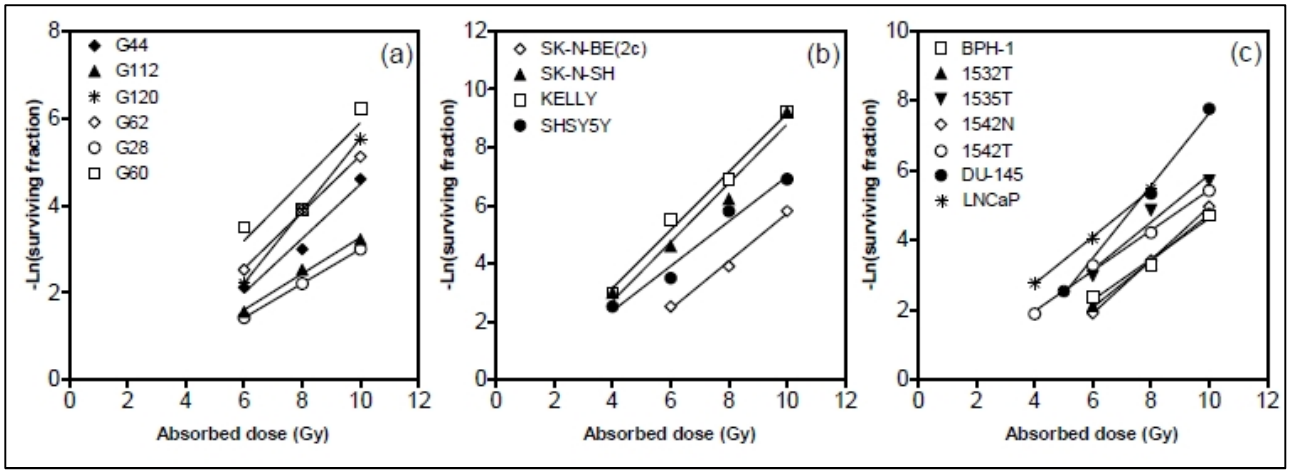

FIG. 1: Plots of the natural logarithm of surviving fraction (for $S_D \leq 0.1$), from historic studies, against absorbed dose for human (a) glioblastoma; (b) neuroblastoma and (c) prostate cell lines.[36-38] Reciprocals of slopes of regression fits represent D_0 as derived from the multi-target formalism (Equation (1)).

Results

The data presented in **Figure 1** represent linear regression fits of the natural logarithm of surviving fraction (for $S_D \leq 0.1$) plotted against absorbed dose. D_0-values derived from the slopes of the regression fits according to Equation (1) for the glioblastoma, neuroblastoma and prostate cell lines emerged as 1.80 ± 0.22 (range: 1.21 – 2.55), 1.13 ± 0.08 (range: 0.99 – 1.30) and 1.45 ± 0.10 (range: 0.96 – 1.73) Gy, respectively.

D_0-values derived from α and β parameters, as described in Equations (4) and (5), are plotted as a function of the log of

cell killing for the glioblastoma cells in **Figure 2**. For comparison, D_0-values determined from **Figure 1** according to the multi-target formalism for all cell lines are also presented. D_0-values derived from the LQ model were found to decrease significantly over cell killing, diminishing from 3.49 ± 0.30 Gy in the first log of cell inactivation to 0.72 ± 0.07 Gy in the 10th log of cell killing (**Figure 2**).

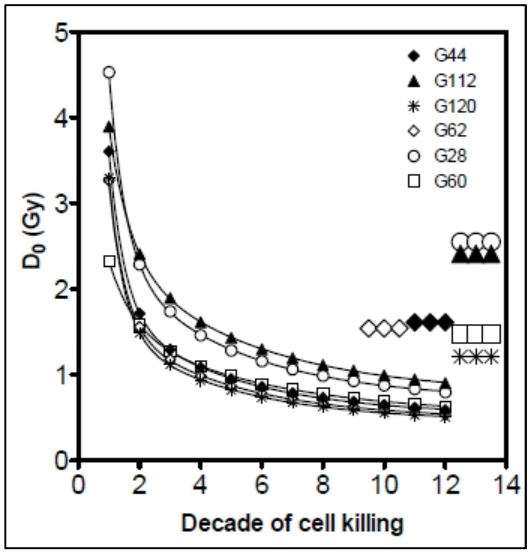

FIG. 2: Plot of D_0, derived from LQ parameters, as a function of the decade of cell killing in which D_0 is derived for 6 human glioblastoma cell lines. D_0 is calculated as the dose required to reduce the cell surviving fraction from: 1.0 to 0.37 (for the first decade of cell killing), 0.1 to 0.037 (for the second decade of cell killing), 0.01 to 0.0037 (for the third decade of cell killing), and so on, using historic α and β parameters.[36, 37] Large symbols represent D_0-values derived from the multi-target formalism.

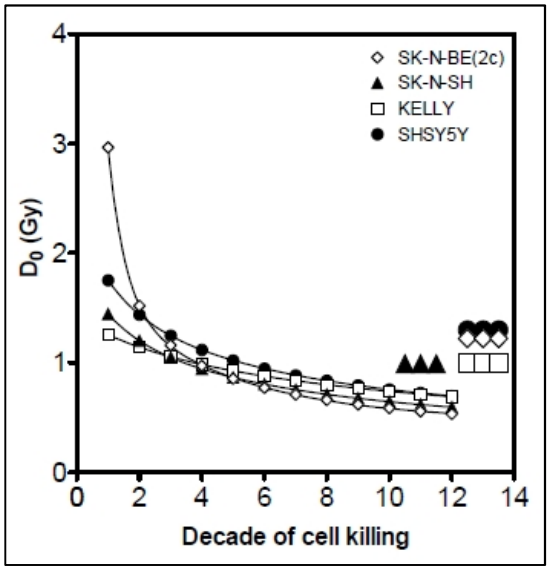

FIG. 3: Plot of D_0, derived from LQ parameters, as a function of the decade of cell killing in which D_0 is derived for 4 human neuroblastoma cell lines. D_0 is calculated as the dose required to reduce the cell surviving fraction from: 1.0 to 0.37 (for the first decade of cell killing), 0.1 to 0.037 (for the second decade of cell killing), 0.01 to 0.0037 (for the third decade of cell killing), and so on, using historic α and β parameters.[36] Large symbols represent D_0-values derived from the multi-target formalism.

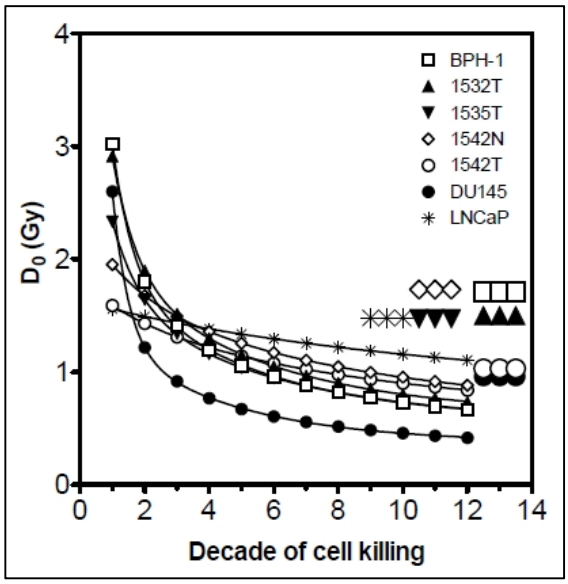

FIG. 4: Plot of D_0, derived from LQ parameters, as a function of the decade of cell killing in which D_0 is derived for human prostate (6 cancer and 1 normal) cell lines. D_0 is calculated as the dose required to reduce the cell surviving fraction from: 1.0 to 0.37 (for the first decade of cell killing), 0.1 to 0.037 (for the second decade of cell killing), 0.01 to 0.0037 (for the third decade of cell killing), and so on, using historic α and β parameters.[37,38] Large symbols represent D_0-values derived from the multi-target formalism.

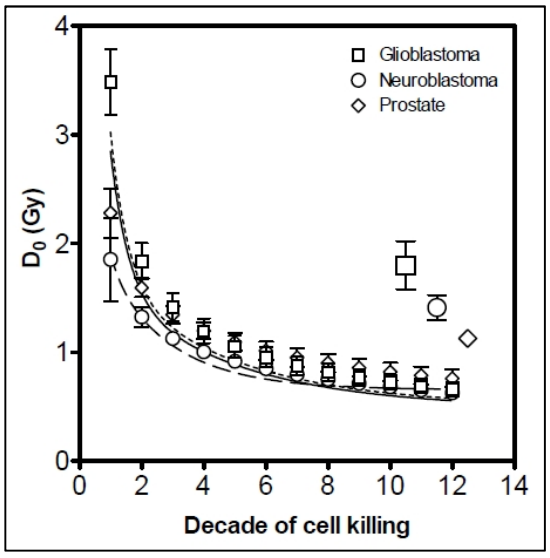

FIG. 5: Plot of D_0, derived from LQ parameters, against the decade of cell killing in which D_0 is derived for human glioblastoma, neuroblastoma, and prostate cell lines. Symbols representing pooled data from **Figures 2-4** are superimposed on fitted curves from historical data for glioblastoma (dotted line)[41], neuroblastoma (dashed line)[31, 43] and prostate (solid line)[44] cell lines. Large symbols represent D_0-values derived from the multi-target formalism from cell survival data for each group of cell lines.[36-38] Error bars represent the standard error of the mean for each set of pooled data.

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Similarly, D_0 declined from 1.85 ± 0.38 to 0.68 ± 0.04 Gy in the neuroblastoma cell lines (**Figure 3**). For the prostate cell lines, D_0 decreased from 2.28 ± 0.23 Gy at high levels of cell survival to 0.81 ± 0.08 Gy at high levels of cell killing (**Figure 4**). In all cases, D_0-values derived from the multi-target formalism were significantly higher than those obtained from the LQ model at a cell survival level of 10^{-10} ($P \leq 0.0023$).

The resulting transition doses obtained from D_0-values derived from the LQ model were found to be up to 3-fold higher than those determined from the multi-target formalism. In the glioblastoma, neuroblastoma and prostate cell lines, the transition doses were found to increase from 7.84 ± 0.56, 8.91 ± 1.20 and 6.55 ± 0.91 Gy to 26.84 ± 2.83, 23.95 ± 2.03 and 22.29 ± 2.31 Gy, respectively.

Discussion

In this study, D_0-values obtained from the multi-target formalism fall within the range of those reported in *in vitro* and *in vivo* studies using cells originating from a wide variety of malignancies.[1,28-35] Although there were changes in rank-order between D_0-values obtained from the multi-target and linear-quadratic (LQ) formalisms, they did not significantly affect the variations of D_0 within each group of cell lines (**Table 1**). Specifically, the coefficients of variation in D_0 for the glioblastoma, neuroblastoma and prostate cell lines emerged as 30.32, 13.88 and 18% for the multi-target model, and 23.86, 12.04 and 26.76% for the LQ model, respectively (**Table 1**). The significant variations demonstrated in D_0 at high levels of cell killing contrast with early suggestions that D_0 for cells from human tumors of varying radiocurability do not differ significantly.[28, 40] These findings may have important implications for the prediction of cellular responses at high radiation absorbed doses for which measurement of cell inactivation is not feasible.

The dependence of D_0 on the extent of cell killing, and therefore total absorbed dose, demonstrated here suggests that D_0-values as obtained from *in vitro* experiments (usually from 2-3 logs of cell killing) or from small *in situ* data sets may be overestimated. With the exception of highly radiosensitive ataxia telangiectasia cells, typical D_0-values for tumor and normal cells have been found to range between ~0.9 and 3.7 Gy.[1, 28-35] To test the strength of our model for extrapolating radiosensitivity at doses for which *in vitro* experimental data cannot be generated, the data presented in **Figures 2-4** were pooled and compared with D_0-values similarly derived from α and β parameters that were reported for glioblastoma, neuroblastoma, and prostate cell lines in other historic studies.[41-44] The comparison is shown in **Figure 5** and illustrates that the current and historical data are congruent. However, the significant reduction seen in D_0 as the level of cell killing increases warrants a re-evaluation of the capacity of the LQ model to predict tissue response at high doses, on the basis of D_0-values derived from the LQ model at cell survival rates of ~10^{10}, instead of those obtained from the multi-target model. For each group of cell lines, the values of D_0 extrapolated in the 10th log of cell killing from the LQ model were again found to be significantly lower than those obtained from the multi-target model. This may have a direct impact on radiotherapy using large fractional doses.

To fully realise the strength of the LQ model in predicting radiation response at doses high enough to yield cell surviving fractions of the order of 10^{-10}, the dose protraction shift parameter, δ[7, 10], should be calculated using values of D_0 from the LQ model (Equations 2-4) corresponding to such high levels of cell killing as defined in Equation (7). High values of D_0 as typically obtained from *in vitro* measurements or limited *in vivo* data can result in large δ-values, and correspondingly lead to low values of the transition dose D^*.[7, 10, 13] To illustrate this, D_0-values were derived from cell survival data using the multi-target model, as defined in Equation (1), and used to calculate δ and D^*.[7,10] They were then compared with those obtained from D_0-values derived within the 10th log of cell killing using the LQ model. On average, D_0-values obtained from the LQ model were found to be about half of those determined from the multi-target model (**Table 1**) or those typically reported in the literature.[1, 28-35] This reduction resulted in a corresponding decrease of 64 – 74% in the shift parameter to values of 0.039 ± 0.003, 0.043 ± 0.004 and 0.049 ± 0.007 Gy^{-1} for the glioblastoma, neuroblastoma and prostate cell lines, respectively (**Table 1**).

The decline in the dose protraction shift parameter translates to ~3-fold increase in the transition dose. The D^*-values obtained here from the multi-target formalism are comparable to those reported by other investigators.[7,10] With the exception of lymphomas and oat cell carcinomas, for which D^* values were very low, average D^* values of 7.8, 5.6, 6.7 and 5.9 Gy were determined for glioblastomas, squamous cell carcinomas, melanomas and adenocarcinomas, respectively.[7] In contrast, D^*-values derived from the LQ model in the 10th log of cell killing are consistent with the suggestion that this formalism is appropriate for assessing tissue response to hypofractionated and stereotactic radiotherapy employing high fractional doses.[4,16] These results demonstrate that the radiation absorbed dose at which the LQ model might not be appropriate for predicting tissue response could be much higher than generally thought. These data further suggest that the LQ model can be used for fractionated radiotherapy employing doses of the order of 20 Gy per fraction.

Conclusion

Using the well-defined α and β parameters of the LQ model for human glioblastoma, neuroblastoma, and prostate cell lines, we provide evidence that the D_0 parameter varies significantly with the level of cell killing. D_0-values derived within the first few logs of cell killing are about 2-fold higher than those obtained at levels of cell killing of the order of 10

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logs. It is further demonstrated that values of the dose protraction shift parameter, δ, are much smaller than initially thought, and can result in significantly larger transition doses D^*. These findings show that the LQ model may be used for fractionated radiotherapy employing large doses per fraction.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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