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Effect of Radiobiological Model Parameterization on Radiotherapy Dose Conversion

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ABSTRACT

The parameterization of radiobiological models is essential to the conversion of the absorbed dose to biological effective dose (BED) and equivalent dose in 2 Gy fractions (EQD2) for clinical radiotherapy applications. In this work, we investigated the uncertainties of the linear quadratic (LQ) model parameters and their effect on the conversion of absorbed dose to BED and EQD2.

The LQ model parameters were fitted using a random sampling method for two experimental datasets, the melanoma and non–small-cell lung cancer (NSCLC) cell lines. Depending on the dose range used in the fitting process, the parameters for the LQ model were α = 0.13 Gy, α/β =2.35 Gy for the dose range 0 – 5.5 Gy and α = 0.22 Gy, α/β = 5.91 Gy for the dose range 0 – 10 Gy for the melanoma survival curve while for the NSCLC cell line, α = 0.33 Gy, α/β = 8.81 Gy for dose range 0 – 6.2 Gy and α = 0.47 Gy, α/β = 27.9 Gy for dose range 0 – 15 Gy, respectively. As a result, the BED and EQD_2 values were converted, based on these LQ parameters differed by up to 100% for a 5-fraction x 10 Gy/fraction hypofractionated dose scheme. It is concluded that radiobiological models should be parameterized based on the dose range and treatment fractionation to reduce the uncertainty of BED and EQD2 conversion.

Keywords: Radiation therapy, radiobiological modeling, linear-quadratic (LQ) model, model parameterization, biological effective dose (BED), equivalent dose in 2Gy fractions (EQD_2)

INTRODUCTION

Radiobiological models are useful tools in the evaluation of therapeutic effects of different radiation treatment doses and fractionation schemes. In conventional radiation therapy the differential response between normal and cancerous tissues is maximized with a clinically achievable treatment dose and fractionation [1,2]. Recent advances in radiotherapy equipment and treatment techniques have also resulted in a paradigm shift from conventionally fractionated radiation therapy (CFRT) that employs small daily doses (1.8 - 4Gy) to hypo-fractionated radiation therapy (HFRT) or stereotactic body radiotherapy (SBRT) that employs ablative doses (8 - 30Gy/fraction). SBRT is an alternative to surgery or

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CFRT for some patients with early stage, localized disease [3-5]. For example, SBRT has been used for primary and metastatic lung and liver malignancies with superior local control and normal tissue toxicities [6-12].

The linear quadratic (LQ) model has been widely used in radiobiological modeling for both radiation research and clinical applications [13,14]. It approximates clonogenic cell survival data with two simple parameters α and β to determine the relative contributions from the linear and quadratic components of the cell survival curve, which have been related to radiation killing due to double and single strand DNA breaks [15]. It gives a good description of the low-dose portion of the cell-survival (the shouldered response) curve for CFRT but over predicts the potency and toxicity for SBRT due to its continuously bending curvature with increasing doses [16-18].

In this work, we investigated the uncertainty of the LQ model parameterization for different dose ranges and its effect on the conversion of absorbed dose to biological effective dose (BED) and equivalent dose at 2Gy fractions (EQD_2) that are used in clinical trial designs and clinical outcome studies [13,14]. A random sampling method is used to fit the LQ model for two experimental datasets, the melanoma and non–small-cell lung cancer (NSCLC) cell lines. For this purpose, a Python program is developed to read the experimental data and to calculate the cell survival based on the LQ model. Model parameters are randomly sampled and the model predictions are compared with the experimental results of the melanoma and NSCLC cell lines to achieve the best fit. The LQ model parameters are then used to convert the physical absorbed dose to BED and EQD_2 for different dose fractionation schemes, and the impact of the dose conversion uncertainties is analyzed.

MATERIALS AND METHODS

The LQ model

The LQ model [13,14] approximates clonogenic cell survival fraction S as:

$S = e^{-\alpha d - \beta d_2}$ (1)

or

$\ln S = -\alpha d - \beta d_2$ (2)

where, d is the absorbed dose in Gy (J/kg), and **α** and β are model parameters that determine the relative contributions from the linear and quadratic components of the cell survival curve, respectively. The parameter α is the slope of the cell survival curve at the limit $d \rightarrow 0$.

Two experimental datasets were used for the parameterization of the LQ model in this work. The first dataset was published by Weichselbaum et al. [19] based on three repeatedly measured x-ray survival fractions of a human melanoma cell line, which has been fitted by Li et al. [20] with $\alpha = 0.13\ Gy^{-1}$ and $\beta = 0.06\ Gy^{-2}$ for CFRT, i.e., the low dose region (d < 5.5 Gy). We further fitted the data for the entire dose range of 0 – 10 Gy. The other dataset was taken from Park et al. [17] , who obtained the value of α and β for the LQ model by determining the arithmetic mean values of each parameter for 12 non-small cell lung cancer (NSCLC) lines from National Cancer Institute [21,22]. The mean value of α and β was 0.333 Gy-1 and $0.0378\ Gy^{-2}$, respectively for CFRT, i.e., for doses below 6.2 Gy. We again fitted the LQ model for the entire dose range to facilitate the dose conversion from CFRT to BED and EQD_2.

The fitting process

A random sampling method [23] was used to determine the model parameters automatically to achieve a good match with the experimental data. A Python computer program was developed to read the experimental data and to calculate the cell survival using the LQ model. The α and β parameters were randomly sampled within their predefined value ranges to ensure adequate parameter selection. The model predictions were compared with the experimental results for all dose-survival inputs. The mean square error (MSE) was used as an objective function to drive the fitting process, i.e.,

$$Objective\ function = \sum_{i=1}^{n} (LnS_{mod}(d_i) - LnS_{exp}(d_i))^2 / n \quad \rightarrow \quad (3)$$

where $S_{mod}(d_i)$ is the model predicted survival fraction value for di and $S_{exp}(d_i)$, the experimental survival fraction value at di, and n is the total number of experimental values. The program stops when a given iteration number or a desired MSE is obtained.

The biologically effective and equivalent dose conversion

In this work, the BED of a given dose fractionation is defined as the total dose required to give the same log cell kill as the fractionation being studied, at an infinitely low dose-rate or with infinitely small fractions well-spaced out; now with an overall time factor for repopulation during continued irradiation [13,14]. Based on the LQ model, BED can be calculated as

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad \rightarrow \quad (4)$$

Where, n is the number of treatment fractions, d is the absorbed dose per fraction in Gy and α/β is the dose at

which the linear and quadratic components of cell kill are equal. Generally, cells with high α/β ratios show a relatively constant rate of cell killing with increasing dose, while those with a low α/β ratio exhibit a pronounced curvature.

In CFRT, the target dose is typically delivered in 2 Gy fractions. Therefore, most clinical outcome data for local tumor control and normal tissue complications were obtained based on treatment results at 2 Gy fractions. For a treatment course with a different fractional dose d, it will be useful to know the equivalent dose of this dose fractionation at 2 Gy fractions, i.e., EQD2. Based on the LQ model and Eq. (4), EQD2 can be calculated as

$$EQD_2 = D \times \left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right) \quad \rightarrow \quad (5)$$

where, D = nd is the total absorbed dose given in Gy. Both BED and EQD2 have been used in designing hypofractionated, especially SBRT clinical trials to set up dose limits for treatment target and organs at risk (OAR) and in their outcome analyses.

RESULTS

Figure 1 shows the survival fractions of a human melanoma cell line irradiated by high-energy photon beams based on three repeated measurements [19]. Also shown are the predicted survival fractions by the LQ model with α = 0.13 Gy−1 and β = 0.0553 Gy−2 (LQ model 1) best fitted for the low dose region (0 to 5.5 Gy) by Li et al. [20]. The LQ model works well for the low dose shoulder and provides a useful α/β ratio for clinical situations in CFRT. However, the LQ model predicts a continuous downward trend for increasing doses, which deviates progressively from the experimental data. We also determined the parameters for the LQ model for the entire dose range from 0 to 10 Gy (LQ model 2). The α and β values are 0.22 Gy^{-1} and 0.0372 Gy^{-2}, which are much greater than those of LQ model 1 with different MSE values (Table 1). As expected, the LQ model predictions show significant deviations from the experimental survival data when fitted either to the low dose range 0 – 5.5 Gy (LQ model 1) or to the entire dose range 0 – 10 Gy (LQ model 2), indicating that the LQ model parameters can be very uncertain depending on the experimental data and fitting methods.

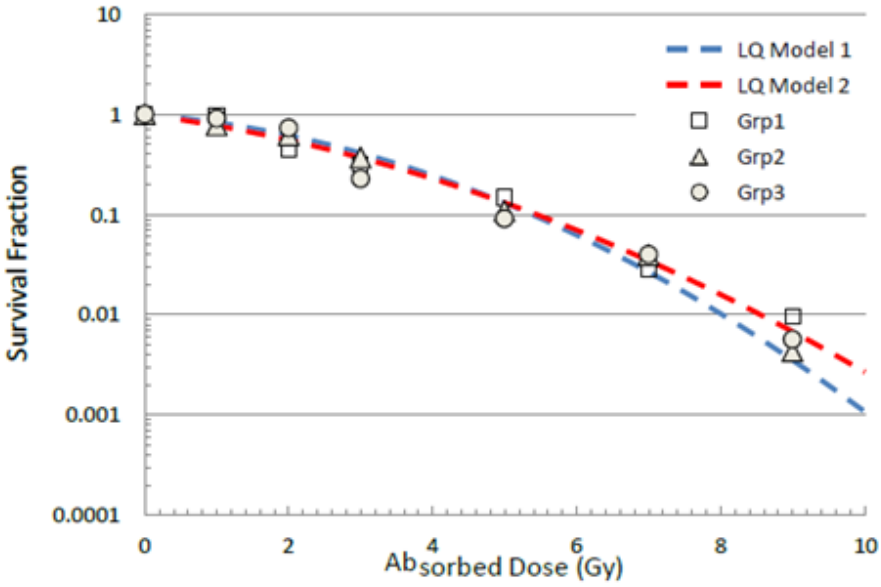

Figure 1: demonstrates the comparison of the LQ model predictions and three sets of measured survival fractions for a human melanoma cell line [19]. The parameters for the LQ model were fitted for dose ranges from 0 to 5.5 Gy (LQ model 1) and from 0 to 10 Gy (LQ model 2), respectively.

For advanced radiotherapy treatment applying either a CFRT schedule or a HFRT schedule such as SBRT, we can calculate BED or EQD_2 using the LQ model parameters derived from the experimental data (e.g. Table 1). In Table 2, we show the BED and EQD_2 values calculated using Eqs. (4) and (5) for the same total absorbed dose of 50 Gy to be delivered CFRT in 25 fractions (2 Gy/fraction), HFRT in 10 fractions (5 Gy/fraction) and SBRT in 5 fractions (10 Gy/fraction). The α and β values for LQ model 1 and LQ model 2 were derived by fitting the survival data to difference dose ranges. The BED values differed by almost 100% and the EQD_2 values differed by more than 40% for the SBRT dose schedule (5 fractions at 10 Gy/fraction) depending on the dose range for model fitting.

Table 1: The parameters for the LQ model and the MSE values for the fitting results. Li et al. [20] fitted the LQ model for the dose range between 0 and 5.5 Gy (LQ model 1). We fitted the LQ model for the entire dose range from 0 to 10 Gy (LQ model 2).

	α Gy^{-1}	**β Gy^{-2}**	**MSE**
This work dose range: 0 – 10Gy	0.22	0.0372	0.0018
Li et al dose range: 0 – 5.5Gy	0.13	0.0553	0.0269

Table 2: The BED and EQD2 values for a total absorbed dose of 50 Gy for different fractionation schedules in 2 Gy, 5 Gy and 10 Gy per fraction using the LQ model parameters fitted to the low-dose range from 0 to 5.5 Gy (Li et al.) and for the entire dose range from 0 to 10 Gy (this work).

	25 x 2Gy/fraction		10 x 5Gy/fraction		5 x 10Gy/fraction	
	BED	EQD_2	BED	EQD_2	BED	EQD_2
This work dose range: 0 – 10Gy	66.91	50	92.27	68.95	134.55	100.34
Li et al. dose range: 0 – 5.5Gy	92.54	50	156.34	84.47	262.68	141.93

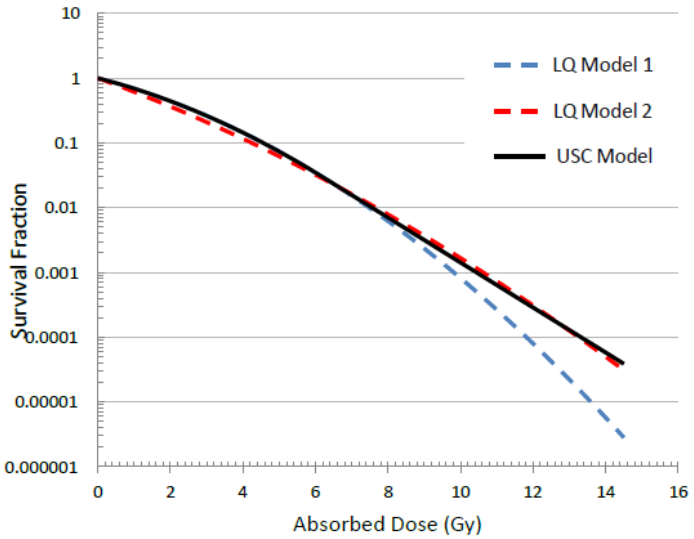

Figure 2: shows the comparison of the LQ and USC model predictions for 12 NSCLC cell lines [17]. The LQ model 1 parameters were taken from Park et al. optimally fitted to the low-dose range with DT = 6.2 Gy. The LQ model 2 parameters were determined for the entire dose range 0 – 15 Gy in this work.

Figure 2 shows the cell survival fractions based on the universal survival curve (USC) model best fitted to 12 NSCLC lines from the US National Cancer Institute by Park et al. [17]. They derived the mean parameter values for the LQ model to fit the low dose survival fraction with $\alpha = 0.333\ Gy^{-1}$ and $\beta = 0.0378\ Gy^{-2}$ (LQ model 1). They also fitted the high dose portion of the survival data to the multi-target (MT) model with Do = 1.25 Gy and n = 4.22. By combining the LQ and MT models at a transition dose, DT = 6.2 Gy, they achieved optimal agreement with the NSCLC data for the entire dose range. We fitted the LQ model to the USC predictions for the entire dose range with $\alpha = 0.471$ Gy-1 and $\beta = 0.0169\ Gy^{-2}$ (LQ model 2). As expected, LQ model 1 shows large deviations at high dose regions with an overall MSE of 0.172 when fitted to the low-dose range 0 – 6.2 Gy. The MSE was reduced to 0.0019 for LQ model 2 when fitted to the entire dose range 0 – 15 Gy (see Table 3). Both LQ model 1 and LQ model 2 showed significant discrepancies from the USC curve, indicating the inabilities of the LQ model to fit both the low-dose shoulder and high-dose straight line at the same time, and the potential uncertainties in the α and β values when model fitting is performed for different dose ranges. In Table 4, the BED and EQD2 values were calculated using Eqs. (4) and (5) for the same total absorbed dose of 50 Gy delivered in 25 fractions (2 Gy/fraction), 10 fractions (5 Gy/fraction) and 5 fractions (10 Gy/fraction). The BED values differed by 57% and the EQD_2 values differed by 37% between LQ model 1 and LQ model 2 for the SBRT dose schedule (5 fractions at 10 Gy/fraction) depending on the dose range for model fitting, indicating potential dose conversion uncertainties for CFRT, HFRT and SBRT outcome analyses.

Table 3: Reveals the parameters for the LQ model and the MSE values to fit the survival fractions of 12 NSCLC cell lines as fitted by Park et al. [17] using their USC model. They fitted the LQ model for the dose range between 0 and 6.2 Gy. We fitted the LQ model for the entire dose range from 0 to 15 Gy.

	α Gy^{-1}	**β Gy^{-2}**	**MSE**
This work dose range: 0 – 15 Gy	0.471	0.0169	0.0019
Park et al. dose range: 0 – 6.2 Gy	0.333	0.0378	0.1720

Table 4: The BED and EQD2 values for a total absorbed dose of 50 Gy for different fractionation schedules in 2 Gy, 5 Gy and 10 Gy per fraction using the LQ model parameters fitted to the dose range from 0 to 6.2 Gy (Park et al.) and for the entire dose range from 0 to 15 Gy (this work).

	25 x 2Gy/fraction		**10 x 5Gy/fraction**		**5 x 10Gy/fraction**	
	BED	**EQD_2**	**BED**	**EQD_2**	**BED**	**EQD_2**
This work dose range: 0 – 15 Gy	53.59	50	58.97	55.02	67.94	63.39
Park et al. dose range: 0 – 6.2 Gy	61.35	50	78.38	63.88	106.75	87.00

DISCUSSION

Radiobiological models are useful tools in modern radiotherapy for the evaluation of biological effects of different treatment plans, dose fractionation schemes and beam modalities. It is used widely in the conversion of a physical quantity (e.g., absorbed dose) to a biological quantity (e.g., BED or EQD_2), which requires good understanding and precise definition [27,28]. Until recently, the LQ model has been the most widely used radiobiological model in radiation research and radiotherapy clinical applications because of its low-dose "shouldered" cell survival predictions and the simple formulas for dose conversion calculation for CFRT, e.g., Eqs. (3) and (4) [13,14]. However, the LQ model often fails to predict the high-dose asymptote; and therefore, overpredicts the potency and toxicity for SBRT [16-18]. In this study, we have investigated the dependence of the LQ model parameterization on the dose range using melanoma and NSCLC cell lines. Our results showed that the LQ model

could not fit the entire dose range well for either cell survival dataset, likely due to the underlying radiobiological assumptions and/or its limited predicting power as a second-order polynomial approximation [16-18,20,24-26,].

The LQ model parameters varied significantly depending on the dose range used in the fitting process. Li et al. [20] showed that $\alpha = 0.13\ Gy^{-1}$ and $\beta = 0.0553\ Gy^{-2}$ resulted in the best agreement with the melanoma survival fractions for the low-dose shoulder (fitting dose range 0 - 5.5 Gy) while our results showed that $\alpha = 0.22\ Gy^{-1}$ and $\beta = 0.0372\ Gy^{-2}$ provided the best fit to the entire dose range of 0 – 10 Gy. This means that for clinical outcome analyses of CFRT with fractional dose < 5.5 Gy, one can use α/β= 2.35 Gy for the BED and EQD2 conversion. However, if one wants to compare HFRT and SBRT outcome results with those of CFRT for doses up to 10 Gy, the α/β ratio has to be increased to 5.91 Gy, based on the model fitting for the entire dose range 0 – 10 Gy, which clearly introduces large inconsistencies in the BED and EQD^2 calculation depending on the actual dose values and α/β ratios applied. As shown in Table 2, the BED and EQD2 values for a 5-fraction x 10 Gy/fraction SBRT schedule are 262.68 Gy and 141.93 Gy, respectively, based on an α/β ratio of 2.35 Gy while they are 134.55 Gy and 100.34 Gy, respectively, based on an α/β ratio of 5.91 Gy. Our results of the NSCLC cell line indicated the same trends as shown in Table 4. Furthermore, the BED or EQD_2 constraints for OARs for such SBRT dose schemes would also be very different if they are converted using α/β ratios derived similarly. Therefore, reliable dosimetric analyses between CFRT, HFRT and SBRT require the use of radiobiological models that can provide accurate dose-survival predictions for large dose ranges.

The LQ formula was first introduced by Sinclair [29] in a review of cell survival curve models in 1966, which was described as an attempt "to fit a mathematical expression to the shape of the curve and see if the result can be interpreted in terms of a model". It was later derived by other investigators from theoretical models of the combination of damage from single- and multi-track events [30,31], which worked well for the shouldered curves of many cell lines and were further developed for radiotherapy applications such as BED and EQD2 conversion [13,14]. The inability of the LQ model to fit both the low-dose shoulder and the high-dose asymptote at the same time for some cell lines was attributed to the second order polynomial approximation of the model [16,17,20,32]. This also seems to be the fundamental reason for the LQ model to have large uncertainties in model parameterization for different dose ranges as shown in this work. Since α determines the initial slope and β affects the final slope of the LQ model predictions, inadequate fitting of the cell survival curve over the entire dose range is likely to produce an α/β ratio that cannot be used for accurate BED and EQD2 calculations.

An ideal radiobiological model should be mathematically capable of fitting the experimental data quite well on the one hand and mechanistic on the other. Without an understanding of the underlying biology, it would be difficult to develop rational links between observations in different systems and to apply our growing knowledge of fundamental radiobiology to better understand and optimize radiotherapy. The LQ model is by far the dominant radiobiological tool used in clinical situations, which enables further discussions on fractionation, tissue sensitivity and effective/equivalent dose conversion based on the use of the α/β ratio [33]. Our results demonstrated that the LQ model parameters could be very uncertain depending on the methods and fitting conditions used in the parameterization process. This is consistent with the findings of van Leeuwen et al. [34] that 75% of the variation in reported estimates for α/β in most cancers between studies was due to inter-study heterogeneity such as patient population, treatment techniques and/or dose fractionation size, rather than expected statistical uncertainty. This variation increased to over 90% when considering studies which directly estimated α and β parameters, indicating the high degree of uncertainty in these factors.

CONCLUSION

In this work, we have investigated the dependence of radiobiological model parameterization on the dose range and its effect on the conversion of absorbed dose to biological effective dose and equivalent dose at 2 Gy fractions for clinical radiotherapy applications. Our results demonstrated that for the melanoma and NSCLC survival datasets investigated, the α and β values were 50- 100% different and the α/β ratio was 100 – 200% different depending on the dose ranges applied. The resulting BED and EGQ_2 converted based on the LQ model parameters were up to 100% different. It is concluded that the LQ model should be parameterized based on the pertinent dose range and dose fractionation to reduce the uncertainty of the α and β factors. Because of the inability of the LQ model to predict both the low-dose shoulder and high-dose asymptote at the same time for some tissues/cell lines the α/β ratios derived for these tissues/cell lines could be very uncertain and should be used with caution in clinical

radiotherapy applications such as for the design of target dose and OAR tolerances for HFRT and SBRT trials using BED and EQD2 conversions, based on the LQ model parameters.

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