

# A Unified Dose Response Relationship to Predict High Dose Fractionation Response in the Lung Cancer Stereotactic Body Radiation Therapy

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## Abstract

**Aim:** This study is designed to investigate the superiority and applicability of the model among the linear-quadratic (LQ), linear-quadratic-linear (LQ-L) and universal-survival-curve (USC) models by fitting published radiation cell survival data of lung cancer cell lines. **Materials and Method:** The radiation cell survival data for small cell (SC) and non-small cell (NSC) lung cancer cell lines were obtained from published reports, and were used to determine the LQ and cell survival curve parameters, which ultimately were used in the curve fitting of the LQ, LQ-L and USC models. **Results:** The results of this study demonstrate that the LQ-L( $D_{t-mt}$ ) model, compared with the LQ and USC models, provides best fit with smooth and gradual transition to the linear portion of the curve at transition dose  $D_{t-mt}$ , where the LQ model loses its validity, and the LQ-L( $D_{t-2\alpha/\beta}$ ) and USC(Dt-mt) models do not transition smoothly to the linear portion of the survival curve. **Conclusion:** The LQ-L( $D_{t-mt}$ ) model is able to fit wide variety of cell survival data over a very wide dose range, and retains the strength of the LQ model in the low-dose range.

**Keywords:** Linear quadratic linear model, linear quadratic model, lung cancer, stereotactic body radiation therapy, universal survival curve model

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## INTRODUCTION

In a standard external beam radiation therapy treatment scheme, dose per fraction between 1.8 Gy to 2.0 Gy is delivered over a period of 5–8 weeks, with 5 fractions/week, which is based on the early experience of radiotherapy treatment and has been justified by accepted radiobiological models.<sup>[1-5]</sup> On the other hand, hypofractionation treatments are delivered to relieve symptoms of the disease, such as pain, by delivering higher doses in few fractions.<sup>[6-8]</sup> Therefore, daily fraction size is larger than that used in standard fractionation, which is commonly more than 3 Gy. Large doses delivered in palliative cases would very unlikely cause late complications as compared to the survival time of the patient.<sup>[9-11]</sup>

Conventionally, single large dose fractions are used by the neurosurgeons to treat brain lesions and it is an important treatment option for patients with benign and metastatic brain lesions.<sup>[12-14]</sup> Similar to stereotactic radiosurgery (SRS),

stereotactic body radiation therapy (SBRT) is a radiation therapy technique in which large dose of radiation is delivered in one or few fractions with high conformity to an extra-cranial body targets.<sup>[15-18]</sup>

Use of large dose fractions in SRS and SBRT defied conventional radiobiology of oxygen-enhanced sensitivity of the tumor cells.<sup>[19]</sup> The large volume tumors comprise of hypoxic core that is more radioresistant due to poor vascular supply to the core.<sup>[20]</sup>

Fractionation schemes are widely used in radiation therapy to exploit the effect of reoxygenation of the tumor cells and sublethal damage repair of normal tissues during interfraction

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interval, which expands the therapeutic window.<sup>[1,21,22]</sup> The radiobiological phenomenon of these fractionation schedules can adequately be explained by the linear quadratic (LQ) model<sup>[23-25]</sup> while it fails to do so for SRS and SBRT due to inherent drawbacks in the formulation.<sup>[25-27]</sup>

In this article, we attempt to investigate the validity and applicability of the LQ, LQ-linear (LQ-L), and universal survival curve (USC) models for lung SBRT using published cell survival data of different cell lines of the lung cancers, and a unified LQ-L model is derived to predict high dose response for lung SBRT cases.

## METHODS AND MATERIALS

### The linear quadratic model

The LQ model is the most popular method used for fitting experimental results derived from *in vitro* and *in vivo* radiation survival experiments of clonogenic cells of mammalian and human origin, irradiated to different dose-fractionation schemes.<sup>[3,23]</sup> Based on the findings of the fits and their agreement with the LQ model predictions, it is widely used in the clinics to interpret tumor and normal tissue response.<sup>[24-27]</sup>

When ionizing radiation interacts with cells, it causes radiation-induced DNA damage, which can be divided into two categories, namely, (1) irreparable lethal damage and (2) repairable sublethal damage.<sup>[25-28]</sup> When single dose of radiation is delivered, the survival fraction (S) is given by

$$S = e^{-\alpha D - \beta D^2} \quad (1)$$

or

$$S = e^{-\alpha(D + \frac{D^2}{\alpha/\beta})} \quad (1a)$$

where D is the single fraction dose,  $\alpha$  and  $\beta$  are the coefficients of lethal and sublethal damages, respectively, and  $\alpha/\beta$  is the tissue-specific parameter that implies the dose at which the components of lethal damage and sublethal damage, i.e.  $\alpha D$  and  $\beta D^2$ , of the LQ survival equation, intersect.

In the formulation of the equation (1) it is assumed that the double-stranded DNA breaks are sufficient enough to cause cell death. The double-stranded breaks can be achieved by single-hit or by two separate hits. The single-hit aberrations correspond to the lethal damage and two separate hits aberrations correspond to the sublethal damage, and are represented by  $\alpha D$  and  $\beta D^2$ , respectively.

The LQ model has been extensively used in clinics over the last three decades, and its validity range appears to extend up to 6 Gy per fraction.<sup>[29]</sup> Beyond the validity range, i.e. at doses more than 6 Gy per fraction which are used in SRS and SBRT treatments. The dose-response curves of the LQ model keep on bending and are inconsistent with the *in vitro* survival curves that are straight on the semilogarithmic plot at high doses.<sup>[30-32]</sup> Hence, the LQ model is a low dose approximation and cannot be applied to interpret dose-response for higher

dose fractionation schedules. At lower single fraction dose, the biologically effective dose (BED) may be given by

$$BED = D(1 + \frac{D}{\alpha/\beta}) \quad (2)$$

Almost a century of the research on the radiobiological basis of radiation therapy revealed 4 Rs that are critical in determining the net effect of radiation therapy on tumor cells: (1) Repair of sublethal damage, (2) Repopulation of cells after irradiation, (3) Redistribution of cells within the cell cycle, and (4) Reoxygenation of the surviving cells during or after irradiation.<sup>[21,22]</sup> The effects of these 4 Rs are exploited in the design of various fractionated treatment schedules. The BED for such a schedule can be written by

$$BED = nd(1 + \frac{nd}{\alpha/\beta}) \quad (3)$$

where n is the number fractions and d is the dose per fraction.

Within the validity range of the LQ model, the comparison of fractionated treatment schedule is done by calculating the equivalent dose in 2 Gy fractions (EQD2) and is given by

$$EQD2 = \frac{BED_x}{(1 + \frac{2}{\alpha/\beta})} \quad (4)$$

where  $BED_x$  is the BED for a fractionated treatment schedule delivered with a dose per fraction "x" other than 2 Gy per fractions.

Conventional treatment protocols are delivered within 4–8 weeks and tumor cell proliferation become an important issue. In formulation or extension of the LQ mode for hypo-fractionation, the issue of tumor cell proliferation is not accounted because it is intended to focus on the investigation of the validity and applicability of the models in the doses used for SRS and SBRT.<sup>[31-35]</sup>

In the high dose range, the sublethal damage repair rate, per lesion, decreases and the production rate of the lethal damage increases with increasing the dose. This phenomenon is explained by various researches, considering high-dose saturation repair models.<sup>[36-41]</sup> This change in repair rate might be due to overloading of the repair enzymes, which may result in a different amount at different dose levels and might increase with increasing dose. Thereby at higher doses, the sublethal damage is not repaired due to overloading of the repair enzymes and hence the LQ model fails to explain dose-response curve.

To explain radiobiological phenomenon, the experimental survival curves and clinical results in the high dose region, the LQ-L, and the USC models were developed by Carlone *et al.*<sup>[34]</sup> and Park *et al.*,<sup>[31]</sup> respectively.

### The linear quadratic-linear model

To address the issue of dose-response at high doses used in SRS and SBRT, Guerrero and Li<sup>[33]</sup> had modified the LQ model, and

subsequently Carlone *et al.*<sup>[34]</sup> explained the LQ-L behavior of the model. Astrahan<sup>[29]</sup> employed bipartite method, proposed by Park *et al.*,<sup>[31]</sup> to the LQ-L model to explain the issues of dose-response occurring at high doses. In the conventional fractionation dose range, the LQ model fits appropriately and smoothly transition to the linearity at some dose  $D_t$ , called transition dose. The survival fraction(s) can be written in bipartite form after single dose of radiation as

$$S = e^{-\alpha(D + \frac{D^2}{\alpha/\beta})} \quad \text{for} \quad D \leq D_t \quad (5a)$$

and

$$S = e^{-\alpha(D_t + \frac{D_t^2}{\alpha/\beta}) - \gamma(D - D_t)} \quad \text{for} \quad D \geq D_t \quad (5b)$$

where  $\alpha$  and  $\alpha/\beta$  are the LQ parameters, as explained in the previous section, and  $\gamma$  is the coefficient of the damage in the final linear portion of the survival curve at high doses.

Equation (5b) reveals that the coefficient “ $\gamma$ ” is the  $\log_e$  cell kill per Gy dose in the linear portion of the survival curve at high doses.

The BED, of the model, can be given by

$$BED = D(1 + \frac{D}{\alpha/\beta}) \quad \text{for} \quad D \leq D_t \quad (6a)$$

and

$$BED = D_t \left(1 + \frac{D_t}{\alpha/\beta}\right) + \frac{\gamma}{\alpha}(D - D_t) \quad \text{for} \quad D \geq D_t \quad (6b)$$

To derive the value of  $\gamma$  or  $\frac{\gamma}{\alpha}$ , let us assume that at a dose of  $D = D_t + \delta D$ , the BED of the LQ model approximately equals to the BED of the LQ-L model, where  $\delta D$  is infinitesimal amount of dose, and the solution is given by equating equations (6a) and (6b) as

$$\frac{\gamma}{\alpha} = 1 + \frac{D + D_t}{\alpha/\beta} \quad (7a)$$

and

$$\frac{\gamma}{\alpha} = 1 + \frac{2D_t}{\alpha/\beta} \quad (\text{for } D = D_t + \delta D = D_t, \text{ limit } \delta D \rightarrow 0) \quad (7b)$$

By substituting equation (7a) into equation (6b), BED can be calculated for SRS/SBRT doses by specifying only one additional parameter, the transition dose  $D_t$ , and the equation (5b) and equation (6b) can be written as

$$S = e^{-\alpha D \left(1 + \frac{2D_t}{\alpha/\beta}\right) + \frac{\alpha D_t^2}{\alpha/\beta}} \quad \text{for} \quad D \geq D_t \quad (7c)$$

and

$$BED = D \left(1 + \frac{2D_t}{\alpha/\beta}\right) - \frac{D_t^2}{\alpha/\beta} \quad \text{for} \quad D \geq D_t \quad (7d)$$

This is a simple expression to calculate BED for high dose single fraction.

Astrahan<sup>[29]</sup> used self-developed software program which allowed interactive manipulation of the  $\alpha$ ,  $\alpha/\beta$  and  $D_t$  parameters of the LQ-L model used in curve fitting for published dose-response and multi fractionation isoeffect data of different cell lines. He saw that the line tangent to the LQ curve at transition dose Gy intersected the  $e^{-\alpha D}$  and  $e^{-\beta D^2}$  curves at dose  $\alpha/\beta$  Gy and also provided closely fit the linear response in the high dose region of some classic *in vitro* cell survival curves for which the value of  $\alpha/\beta$  was low.<sup>[29]</sup> This value of  $D_t$  hereinafter will be denoted by  $D_{t-2\alpha/\beta}$ . For fractionated regimen where treatment is delivered in n number of fractions with D per fraction, the S and the BED can be written as

$$S = e^{-\alpha n(D + \frac{D^2}{\alpha/\beta})} \quad \text{for} \quad D \leq D_t \quad (8a)$$

and

$$S = e^{-n \left[1 - \alpha D \left(1 + \frac{2D_t}{\alpha/\beta}\right) + \frac{\alpha D_t^2}{\alpha/\beta}\right]} \quad \text{for} \quad D \geq D_t \quad (8b)$$

$$BED = nD \left(1 + \frac{D}{\alpha/\beta}\right) \quad \text{for} \quad D \leq D_t \quad (8c)$$

and

$$BED = nD \left(1 + \frac{2D_t}{\alpha/\beta}\right) - \frac{nD_t^2}{\alpha/\beta} \quad \text{for} \quad D \geq D_t \quad (8d)$$

The EQD2 for high dose fractionation regimen is given by

$$EQD2 = \frac{nD \left(1 + \frac{2D_t}{\alpha/\beta}\right) - \frac{nD_t^2}{\alpha/\beta}}{\left(1 + \frac{2}{\alpha/\beta}\right)} \quad \text{for} \quad D \geq D_t \quad (9)$$

### The universal survival curve model

The experimental data for various cell lines have shown that there is a linear relationship between dose and log of the survival fraction at higher doses. The LQ model calculations predict a continuous bending of the survival curve, which reveals that the LQ model overestimates the effect in high dose region, because of its inability to account for the saturation of the repair of sublethal damage. The multi-target multi-hit (MT) model proposed by Tym and Todd<sup>[42]</sup> to fit survival curve data for different cell lines, provides a best fit. The survival fraction following a dose D is given by

$$S = e^{-D/D_1} \left[1 - \left(1 - e^{-D/D_0}\right)^{\bar{n}}\right] \quad (10)$$

where the first term,  $e^{-D/D_1}$  represents a single event to be responsible for an effect, corresponding to the lethal damage of the LQ model, and the second term in the square bracket,  $\left[1 - \left(1 - e^{-D/D_0}\right)^{\bar{n}}\right]$ , represents that  $\bar{n}$  independent events are

responsible to cause an effect, that is corresponding to the sublethal damage of the LQ model. The  $D_1$  and  $D_0$  are the initial slope (first log cell kill) and final slope (constant fraction log cell kill) of survival curve, respectively.

In the low dose region where  $D \ll D_0$  and  $D \rightarrow 0$ , the expression in equation (10) reduces to

$$S = e^{-D/D_1} \quad (11)$$

By comparing equation (11) with the first term of the LQ model (equation (1)), we have  $\frac{1}{D_1} = \alpha$ . Using the value of  $\frac{1}{D_1}$  into equation (10), the MT model can be written as

$$S = e^{-\alpha D} \left[ 1 - \left( 1 - e^{-D/D_0} \right)^{\bar{n}} \right] \quad (12)$$

In the high dose region, where  $D \gg D_0$ , the survival curve of the MT model approaches an asymptote and is given by

$$S = (n)e^{(-D/D_0)} \quad (13)$$

or

$$S = e^{\left[ -D/D_0 + \ln(\bar{n}) \right]} \quad (14)$$

Park *et al.*<sup>[31]</sup> have proposed a hybrid model, the USC model, by combining the LQ model and the MT model to enhance the fit of the survival curve data in a larger span.

In the USC model, the LQ model smoothly transitions into the asymptotic linear portion of the MT model at a transition dose  $D_t$ . Hence, the USC model for single dose fraction is given by

$$S = e^{-\alpha(D + \frac{D^2}{\alpha/\beta})} \quad \text{for } D \leq D_t \quad (15a)$$

and

$$S = e^{-D/D_0 + \ln(\bar{n})} \quad \text{for } D \geq D_t \quad (15b)$$

The BED for single dose fraction scheme is

$$BED = D \left( 1 + \frac{D}{\alpha/\beta} \right) \quad \text{for } D \leq D_t \quad (16a)$$

and

$$BED = \frac{1}{\alpha D_0} \left[ D - D_0 \ln(\bar{n}) \right] \quad \text{for } D \geq D_t \quad (16b)$$

In equation (15b) and equation (16b),  $\ln(\bar{n})$  is the asymptotic intercept on y-axis, and can be derived by equating equation (16a) with equation (16b) at the transition dose  $D_t$

$$\ln(\bar{n}) = \frac{Dt}{D_0} - \alpha Dt \left( 1 + \frac{Dt}{\alpha/\beta} \right) \quad (16c)$$

By substituting equation (16c) into equations (15b) and (16b), S and BED can be calculated for SRS/SBRT doses by

specifying only two additional parameters, the transition dose  $D_t$  and  $D_0$ . equation (16b) can be written as

$$S = e^{-\frac{1}{D_0}(D-Dt) - \alpha Dt \left( 1 + \frac{Dt}{\alpha/\beta} \right)} \quad \text{for } D \geq D_t \quad (16d)$$

and

$$BED = \frac{1}{\alpha D_0} (D - Dt) + Dt \left( 1 + \frac{Dt}{\alpha/\beta} \right) \quad \text{for } D \geq D_t \quad (16e)$$

For multiple fractionation schemes, where n number of fractions are delivered with D(Gy) per fraction, the S for the USC model is given by

$$S = e^{-n\alpha(D + \frac{D^2}{\alpha/\beta})} \quad \text{for } D \leq D_t \quad (17a)$$

and

$$S = e^{n \left[ -\frac{1}{D_0}(D-Dt) - \alpha Dt \left( 1 + \frac{Dt}{\alpha/\beta} \right) \right]} \quad \text{for } D \geq D_t \quad (17b)$$

The BED for such fractionated scheme is

$$BED = nD \left( 1 + \frac{D}{\alpha/\beta} \right) \quad \text{for } D \leq D_t \quad (18a)$$

and

$$BED = \frac{n}{\alpha D_0} (D - Dt) + nDt \left( 1 + \frac{Dt}{\alpha/\beta} \right) \quad \text{for } D \geq D_t \quad (18b)$$

The EQD2 for high dose fractionation regimen is given by

$$EQD2 = \frac{\frac{n}{\alpha D_0} (D - Dt) + nDt \left( 1 + \frac{Dt}{\alpha/\beta} \right)}{\left( 1 + \frac{2}{\alpha/\beta} \right)} \quad \text{for } D \geq D_t \quad (19)$$

### Unified linear quadratic-linear model

Park *et al.*<sup>[31]</sup> determined the  $D_t$  at which the S of the LQ model smoothly transitions into an asymptotic straight line of the S of the MT model, which is a tangential line to the LQ curve. At  $D_t$ , the S of the LQ model is equal to that of the MT model, hence by equating equation (15a) to equation (15b), or equation (16a) to (16b) at transition dose, the  $D_t$  can be given by

$$D_{t-mt} = \frac{2D_0 \ln(\bar{n})}{(1 - \alpha D_0)} \quad (20)$$

where  $D_{t-mt}$  is the transition dose derived using the MT model. At  $D_{t-mt}$ , the S of the LQ model also smoothly transitions into an asymptotic straight line of the S of the LQ-L model, which is tangential line to the LQ curve, and hence at this point of dose the S of the LQ model is equal to the S of the LQ-L model. Consequently, at transition dose  $D_t$ , the survival fractions of these three models are equal. Therefore,  $D_{t-mt}$  from Eq.(20) can be used into equation (7c) and equation (7d) to describe the S and BED for high dose fraction schemes.

### Data collection

Seven and 15 *in vitro* radiation survival plots for human lung cancer cell lines were digitized from the charts of reports of Carney *et al.*,<sup>[43]</sup> consisting of 5 small cell (SC) and 2 large cell (LC) lines, and Carmichael *et al.*,<sup>[44]</sup> consisting of 3 SC, 3 LC, 4 adenocarcinoma (Ad), 3 adenosquamous (AdSq) and 2 squamous (Sq) cell lines, respectively. In both the reports the charts had been plotted with more than one experimental data. Hence, the digitized data were averaged for same dose point. The cell survival parameters,  $D_0$  and  $\bar{n}$ , and the LQ parameters,  $\alpha$  and  $\beta$ , were extracted from the reports of Carmichael *et al.*<sup>[44]</sup> for 8 SC and 12 non-SC (NSC), and Krarup *et al.*<sup>[45]</sup> for 15 SC cell lines. The plots, the cell survival and the LQ parameters were grouped into two classes of SC and NSC lung cancer cell lines. The LC, Ad, AdSq and Sq lung cancer cell lines are the parts of NSC lung cancer cell lines, but to avoid confusion between data sets of different researchers, we used same terminology as was used by original investigator.

### RESULTS

The value of the LQ model parameter,  $\alpha$ , for digitized cell survival data from the charts of the reports of Carney *et al.*<sup>[43]</sup> and Carmichael *et al.*,<sup>[44]</sup> was determined by the best-fit regression method for low-dose survival data and  $\beta$  was calculated with an interactive inspection and chi-square best fit to the initial curvature points with  $R^2 \geq 0.97$ . The values of  $D_0$  and  $\bar{n}$  were calculated by the best-fit regression method to the final slope survival data, and are used in equation (20)

to calculated transition doses. Table 1 enlists the LQ and radiation cell survival parameters for SC and NSC lines.

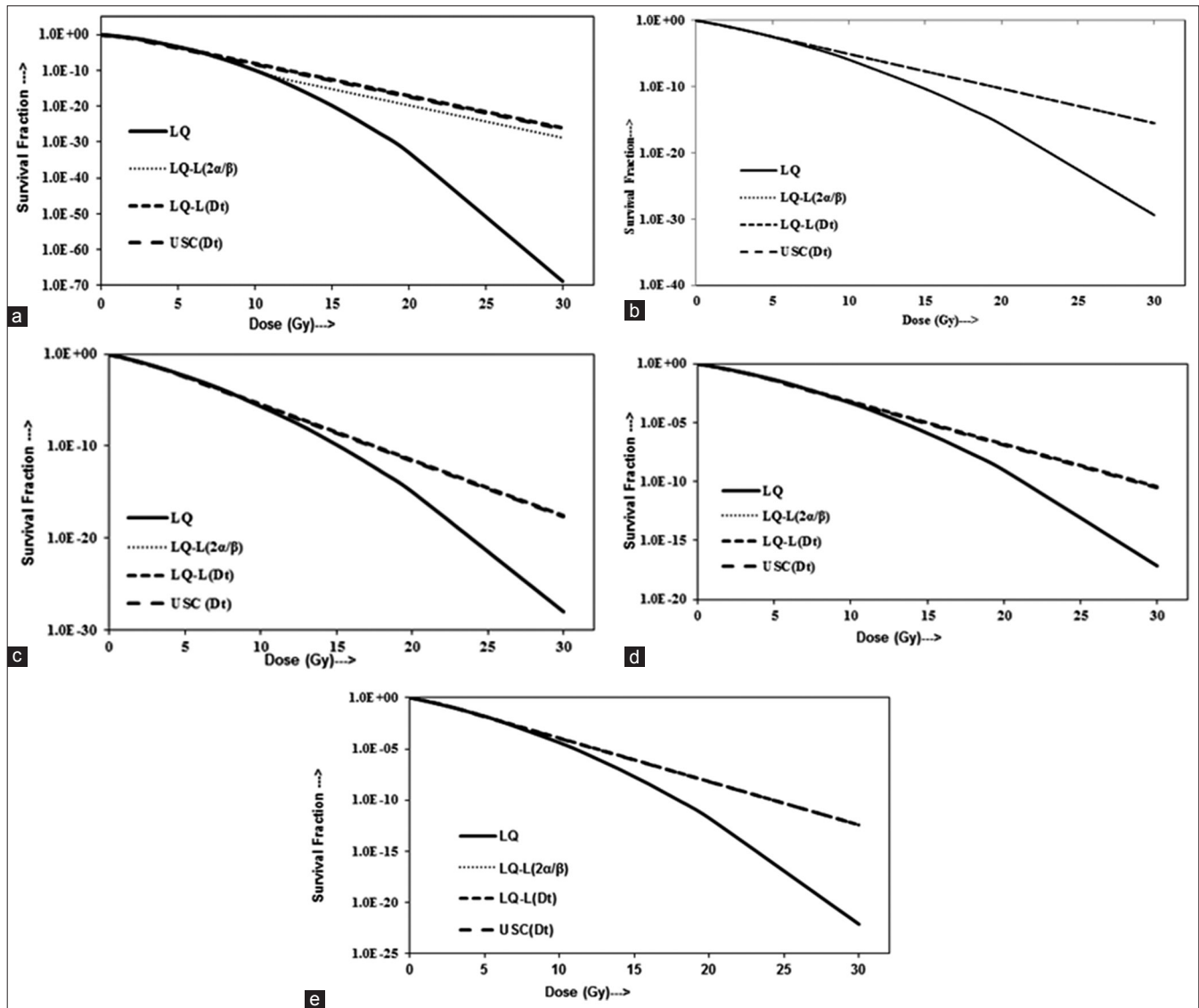
The parameters from Table 1 were used to calculate the values of  $D_{t-2\alpha/\beta}$  and  $D_t=[(2D_0 \ln(\bar{n}))/((1-\alpha)D_0)]$ , for digitized data set of the reports,<sup>[43,44]</sup> and to plot survival curves for the LQ, LQ-L, and USC models over the extrapolated range up to 30 Gy, shown in Figures 1-7. Two set of SF curves were plotted for the LQ-L model for transition dose denoted by  $D_{t-2\alpha/\beta}$  and  $D_{t-mt}$  with same value of  $\gamma (=1/D_0)$ , while for the USC model it was done only for  $D_{t-mt}$ .

The mean values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$ , determined from the digitized data of Carney *et al.*'s report,<sup>[43]</sup> were found to be  $0.75 \pm 0.17 \text{ Gy}^{-1}$  (ranged: 0.49–0.92  $\text{Gy}^{-1}$ ),  $0.06 \pm 0.05 \text{ Gy}^{-2}$  (ranged: 0.03–0.15  $\text{Gy}^{-2}$ ),  $0.85 \pm 0.28 \text{ Gy}$  (ranged: 0.48–1.20 Gy, and  $3.1 \pm 1.93$  (ranged: 1.58–6.2), respectively, for SC cell lines;  $0.13 \pm 0.03 \text{ Gy}^{-1}$  (ranged: 0.11–0.15  $\text{Gy}^{-1}$ ),  $0.10 \pm 0.01 \text{ Gy}^{-2}$  (ranged: 0.10–0.11  $\text{Gy}^{-2}$ ),  $0.83 \pm 0.06 \text{ Gy}$  (ranged 0.79–0.87 Gy) and  $11.94 \pm 5.10$  (ranged 8.33–15.54), respectively, for LC cell lines. The mean values of these parameters for digitized data of Carmichael *et al.*'s report<sup>[44]</sup> were  $0.16 \pm 0.12 \text{ Gy}^{-1}$  (ranged: 0.07–0.30  $\text{Gy}^{-1}$ ),  $0.06 \pm 0.03 \text{ Gy}^{-2}$  (ranged 0.04–0.09  $\text{Gy}^{-2}$ ),  $1.41 \pm 0.42 \text{ Gy}$  (ranged: 0.98–1.81 Gy) and  $4.59 \pm 1.18$  (ranged 3.2–6.6), respectively, for SC cell lines;  $0.20 \pm 0.05 \text{ Gy}^{-1}$  (ranged: 0.15–0.24  $\text{Gy}^{-1}$ ),  $0.06 \pm 0.03 \text{ Gy}^{-2}$  (ranged: 0.04–0.10  $\text{Gy}^{-2}$ ),  $1.18 \pm 0.28 \text{ Gy}$  (ranged: 0.91–1.47 Gy) and  $7.22 \pm 2.79$  (ranged: 5.28–10.42), respectively, for LC cell lines;  $0.39 \pm 0.30 \text{ Gy}^{-1}$  (ranged: 0.14–0.79  $\text{Gy}^{-1}$ ),  $0.04 \pm 0.01 \text{ Gy}^{-2}$  (ranged 0.02–0.06  $\text{Gy}^{-2}$ ),

**Table 1: Linear quadratic and radiation cell survival parameters for 22 human lung cancer cell lines**

Serial number	Type	Cell line	$\alpha$ (/Gy)	$\beta$ (/Gy <sup>2</sup> )	$D_0$ (Gy)	$\bar{n}$	Reference
1	SC	NCI H146	0.79	0.15	0.48	6.20	[43]
2	SC	NCI H249	0.92	0.05	0.83	1.58	[43]
3	SC	NCI H187	0.87	0.04	0.71	3.70	[43]
4	SC	NCI H209	0.49	0.03	1.20	2.37	[43]
5	SC	NCI H69	0.67	0.03	1.03	1.65	[43]
6	SC	NCI H69 classic	0.30	0.09	0.98	4.00	[44]
7	SC	NCI H526 variant	0.07	0.04	1.81	3.82	[44]
8	SC	NCI H841 variant	0.11	0.04	1.44	5.95	[44]
9	LC	NCI H82	0.15	0.10	0.79	15.54	[43]
10	LC	NCI H417	0.11	0.11	0.87	8.33	[43]
11	LC	NCI H157	0.24	0.06	1.17	5.95	[44]
12	LC	NCI H460	0.19	0.10	0.91	10.42	[44]
13	LC	NCI H661	0.15	0.04	1.47	5.28	[44]
14	Ad	NCI H23	0.79	0.04	1.02	1.28	[44]
15	Ad	NCI H358	0.43	0.02	1.08	9.13	[44]
16	Ad	NCI H522	0.14	0.06	1.09	8.03	[44]
17	Ad	A549	0.19	0.04	1.82	2.38	[44]
18	AdSq	NCI H322	0.28	0.05	1.01	7.00	[44]
19	AdSq	NCI H596	0.16	0.05	1.25	4.99	[44]
20	AdSq	NCI H647	0.31	0.10	1.48	2.04	[44]
21	Sq	NCI H226	0.28	0.03	1.16	9.03	[44]
22	Sq	NCI H520	0.29	0.06	0.97	6.84	[44]

SC: Small cell lung cancer, Ad: Adenocarcinoma cell lung cancer, AdSq: Adenosquamous cell lung cancer, Sq: Squamous cell lung cancer, LC: : Large cell lung cancer



**Figure 1:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for small cell lung cancer cell lines data digitized from Carney *et al.*'s charts<sup>[43]</sup>

1.25 ± 0.38 Gy (ranged: 1.02–1.82 Gy) and 5.21 ± 3.95 (ranged: 1.28–9.13), respectively, for Ad cell lines; 0.25 ± 0.08 Gy<sup>-1</sup> (ranged 0.16–0.31 Gy<sup>-1</sup>), 0.07 ± 0.03 Gy<sup>-2</sup> (ranged: 0.05–0.10 Gy<sup>-2</sup>), 1.25 ± 0.24 Gy (ranged: 1.01–1.48 Gy) and 4.68 ± 2.49 (ranged: 2.04–7.0), respectively, for AdSq cell lines; 0.29 ± 0.01 Gy<sup>-1</sup> (ranged: 0.28–0.29 Gy<sup>-1</sup>), 0.05 ± 0.02 Gy<sup>-2</sup> (ranged: 0.03–0.06 Gy<sup>-2</sup>), 1.07 ± 0.13 Gy (ranged: 0.97–1.16 Gy) and 7.94 ± 1.55 (ranged: 6.86–9.03), respectively, for Sq cell lines.

Combined calculated values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  parameters for SC and NSC cell lines for digitized data of both reports of Refs 43 and 44, are compared with that of extracted from the reports of Refs. 44 and 45, shown in Table 2, with Student's *t*-test values.

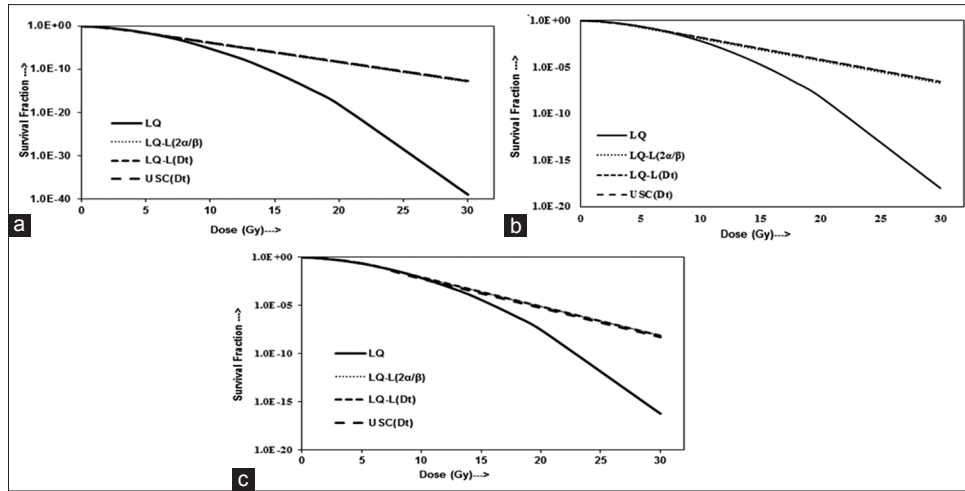
Further the calculated values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  are combined with that of obtained from the reports, to get representative values of the parameters and are given in Table 3 along with calculated values of  $D_{t-mt}$ .

The parameters from Table 3 were used to plot survival curves for the LQ, LQ-L( $D_{t-2\alpha/\beta}$ ), LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) models, shown in Figures 8 and 9 for SC and NSC cell lines, respectively.

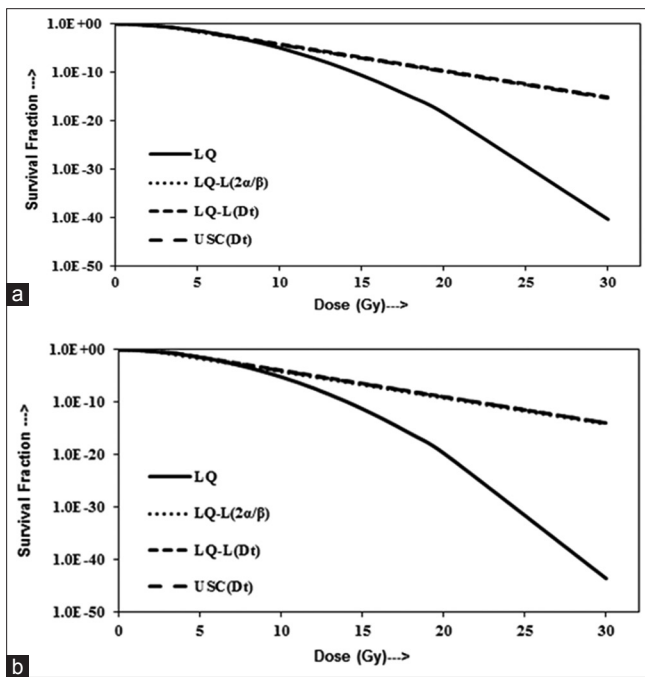
The BED and EQD2 were calculated for fractionated SBRT dose scheme of the RTOG 0813<sup>[46]</sup> protocol from Level 1 to Level 9 (8 Gy to 12 Gy per fraction delivered in 5 fractions) using the LQ, LQ-L( $D_{t-mt}$ ) and USD( $D_{t-mt}$ ) models, for SC and NSC lung cancers. The values of representative parameters [Table 3] are used and are given in Table 4.

## DISCUSSION

The LQ model is well documented in the literature that it adequately describe the survival curve in low dose fraction domain, and hence is regarded as a low dose approximation to the equation,<sup>[25]</sup> in which the intrinsic radiosensitivity of the cells is represented by



**Figure 2:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for small cell lung cancer cell lines data digitized from Carmichael *et al.*'s charts<sup>[44]</sup>



**Figure 3:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for large cell lung cancer cell lines data digitized from Carney *et al.*'s charts<sup>[43]</sup>

the coefficient of lethal damage,  $\alpha$  which is the initial slope of the survival curve.<sup>[47]</sup> Beyond the LQ model dose fraction domain, i.e. in the high dose fraction domain, an exponential function fit radiation cell survival data of most of the cell lines, and represented by the parameters,  $D_0$  and  $\bar{n}$ . In Table 1, the LQ and radiation cell survival parameters for SC and NSC lines, differ than that in the original report, because of an inaccuracy occurred in the digitization of the data from the charts and the methods used by the authors.<sup>[43,44]</sup> The parameters derived by Carney *et al.*<sup>[43]</sup> employing linear regression analysis of the exponential region of the curve and Carmichael *et al.*<sup>[44]</sup> derived by fitting to the LQ and single-hit, MT models using a program written by Albright.<sup>[48]</sup>

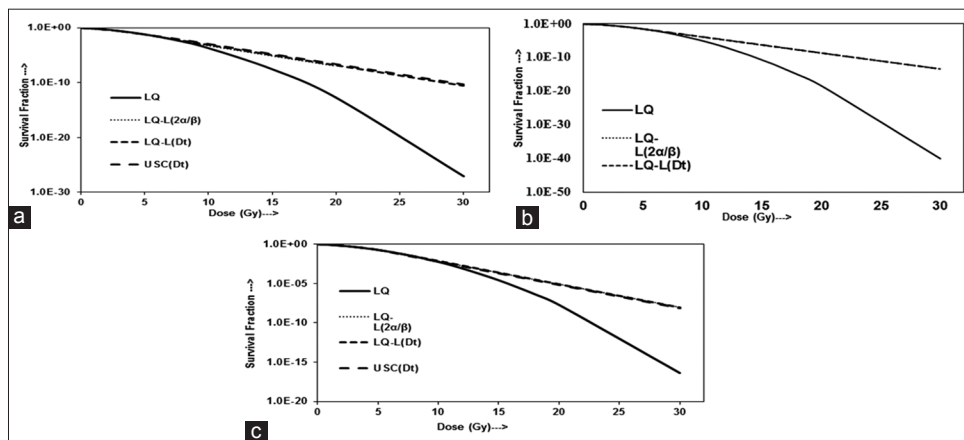
It is seen in Table 1 that the radiation survival curves for the SC of Carney *et al.*'s charts<sup>[43]</sup> characterized by  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  are considerably different than that of the counterpart SC of Carmichael *et al.*'s,<sup>[44]</sup> except for NCI H 146. For NSC, comprising LC, Ad, AdSq and Sq cell lines, the survival curve for LC of Carney *et al.*'s data<sup>[43]</sup> characterized by  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  are comparable to their counterparts in Carmichael *et al.*'s data.<sup>[44]</sup> Intra-comparison of the parameters of Carmichael *et al.*<sup>[44]</sup> data, show that the values for Ad are comparable with that of AdSq and Sq, except for NCI H 23 and NCI H 358.

The values of  $\alpha$ ,  $\beta$ ,  $D_0$ , and  $n$ , for each cell line, were used to calculate the values of  $D_{t-2}\alpha/\beta$  and  $D_t [(2D_0 \ln(n-))/(1-\alpha D_0)]$ , for digitized data set of the reports,<sup>[43,44]</sup> which were further used to plot survival curves for the LQ, LQ-L, and USC models, and the comparison of the goodness of fit with the digitized and extrapolated survival data was performed using the Chi-square goodness test. The LQ parameters  $\alpha$  and  $\beta$  for 6 cell lines, 4 SC (NCI H249, NCI H187, NCI H209, NCI H69) and 2 Ad (NCI H23, NCI H358), provide higher values of  $D_{t-2}\alpha/\beta$ , than the dose range considered in this study, resulting in the LQ-L( $D_{t-2}\alpha/\beta$ ) curves to superimpose on the LQ curves, shown in Figures 1b-e and 5a, b. A close inspection of Figures 1a (NCI H146), 2a (NCI H69 classic), 2b (NCI H526 variant), 3b (NCI H417), 4a (NCI H157), 5d (A549), 6a (NCI H322), 6b (NCI H596), 6c (NCI H647), and 7b (NCI H520) make clear that when  $D_{t-2}\alpha/\beta$  is close to  $D_{t-mt}$  the LQ-L( $D_{t-2}\alpha/\beta$ ) curve runs parallel to the LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) curves. It has also been seen that as  $D_{t-mt}/D_{t-2}\alpha/\beta$  ratio tends to reach 1, the LQ-L( $D_{t-2}\alpha/\beta$ ) curve approaches close to the LQ-L( $D_{t-mt}$ ) curve. On the other hand, in Figures 1b (NCL H249) and 2a (NCI H69 classic), the USC( $D_{t-mt}$ ) curves superimposed on the LQ-L( $D_{t-mt}$ ) curves. In Figures 2b (NCI H 526 variant), 4a (NCI H157), 4b (NCI H46), 5a (NCI H23), 5d (A549), and 6c (NCI H647) the USC curves are slightly raised at  $D_{t-mt}$  i. e. the value of survival fraction slightly increased at  $D_{t-mt}$  and then progress parallel to the LQ-L( $D_{t-mt}$ ). Figures 1a-e, 2c, 3a-b, 4c, 5b-c, 6a-b and 7a-b show that the USC curves drop slightly at

**Table 2: Linear quadratic and radiation survival parameters for combined data set**

Cell type	Type of data	Statistical function	$\alpha$ (/Gy)	$\beta$ (/Gy <sup>2</sup> )	$D_0$ (Gy)	$\bar{n}$
SC	LQ and cell survival parameters calculated from digitized data <sup>[43,44]</sup>	Mean±SD	0.46±0.23	0.08±0.04	1.04±0.29	3.97±3.63
		95% CI	0.46±0.09	0.08±0.02	1.04±0.12	3.97±1.48
		Range	0.02-0.87	0.005-0.17	0.65-1.5	1.00-17.70
	LQ and cell survival parameters obtained from published reports <sup>[44,45]</sup>	Mean±SD	0.53±0.34	0.06±0.04	1.06±0.42	3.66±1.77
		95% CI	0.53±0.23	0.06±0.03	1.06±0.29	3.66±1.22
		Range	0.07-0.92	0.03-0.15	0.48-1.81	1.58-6.20
	<i>P</i> ( <i>t</i> -student test)	0.59	0.33	0.92	0.76	
NSC	LQ and cell survival parameters calculated from digitized data <sup>[43,44]</sup>	Mean±SD	0.33±0.21	0.04±0.02	1.25±0.21	4.88±2.39
		95% CI	0.33±0.12	0.04±0.01	1.25±0.12	4.88±1.20
		Range	0.08-0.89	0.01-0.10	1.00-1.60	1.20-9.50
	LQ and cell survival parameters obtained from published reports <sup>[44,45]</sup>	Mean±SD	0.27±0.17	0.06±0.03	1.15±0.28	6.87±3.75
		95% CI	0.27±0.09	0.06±0.02	1.15±0.15	6.87±1.96
		Range	0.11-0.79	0.02-0.11	0.79-1.82	1.28-15.54
	<i>P</i> ( <i>t</i> -student test)	0.41	0.07	0.31	0.11	

SC: Small cell lung cancer, NSC: Nonsmall cell lung cancer, LQ: Linear quadratic, CI: Confidence interval, SD: Standard deviation



**Figure 4:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for large cell lung cancer cell lines data digitized from Carmichael *et al.*'s charts<sup>[44]</sup>

$D_{t-mt}$  and then run parallel with LQ-L( $D_{t-mt}$ ) curves. It is clear from Figures 1-7 that the LQ-L( $D_{t-mt}$ ) curves, for cell lines studied in this work, do not show any raise or drop at  $D_{t-mt}$  and transition smoothly to the linear asymptotic portion of the curve over the range of the dose fraction accounted in this study.

Combined calculated values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  parameters for SC and NSC cell lines for digitized data of both reports, of Refs 43 and 44, are compared with that of extracted from the reports, of Refs 44 and 45, and are shown in Table 2. The Student's *t*-test reveals that the calculated values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  are not significantly different than that of the values obtained from the reports. Since, the Student's *t*-test illustrates no statistical difference between the parameters of two groups, the calculated values of  $\alpha$ ,  $\beta$ ,  $D_0$  and  $\bar{n}$  are combined with that obtained from the reports, and the results are given in Table 3. The value of  $D_{t-mt}$  and  $D_0$  [Table 3] are comparable, while values of  $\alpha$ ,  $\alpha/\beta$  and  $\bar{n}$  are different from that reported by Wennberg and Lax<sup>[49]</sup> for lung tumors, which were of NSC taken from Park *et al.*<sup>[31]</sup>

Using resultant values of the parameter, the representative values the LQ and survival curve parameters, with calculated

$D_{t-mt}$  are given in Table 3. Figures 8 and 9 show the plots for the LQ, LQ-L( $D_{t-2\alpha/\beta}$ ), LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) models for representative values [Table 3] of  $\alpha$ ,  $\beta$ ,  $\alpha/\beta$ ,  $D_0$ ,  $\bar{n}$  and  $D_{t-mt}$  for SC and NSC cell lines, respectively. In Figures 8 and 9, the LQ-L( $D_{t-mt}$ ) curves, for both cell lines, transition smoothly to asymptotic linear portion at  $D_{t-mt}$ , while the USC( $D_{t-mt}$ ) curves show slight increase in survival fraction at  $D_{t-mt}$ . In Figure 8 the LQ-L( $D_{t-2\alpha/\beta}$ ) curve follows the LQ curve, even after passing initial slope of the curve, and then transitions to a linear portion with a significant increase in survival fraction which makes it bi-phasic, due to considerably higher value of  $D_{t-2\alpha/\beta}$  than  $D_{t-mt}$ . On the other hand, in Figure 9, for NSC cell lines, the LQ-L( $D_{t-2\alpha/\beta}$ ) curve drops at  $D_{t-2\alpha/\beta}$  that brings it below the LQ curve, and then intersects the LQ curve. The steepness of the survival curves of these models varied considerably at dose per fraction above transition dose and LQ-L( $D_{t-mt}$ ) model showed smooth transition than the USC and the LQ-L( $D_{t-2\alpha/\beta}$ ) models. For some of the cell lines, the USC model is slightly less sensitive compared to the LQ-L( $D_{t-mt}$ ) model, considerably less sensitive to the LQ-L( $D_{t-2\alpha/\beta}$ ) and the LQ models at high fraction doses.

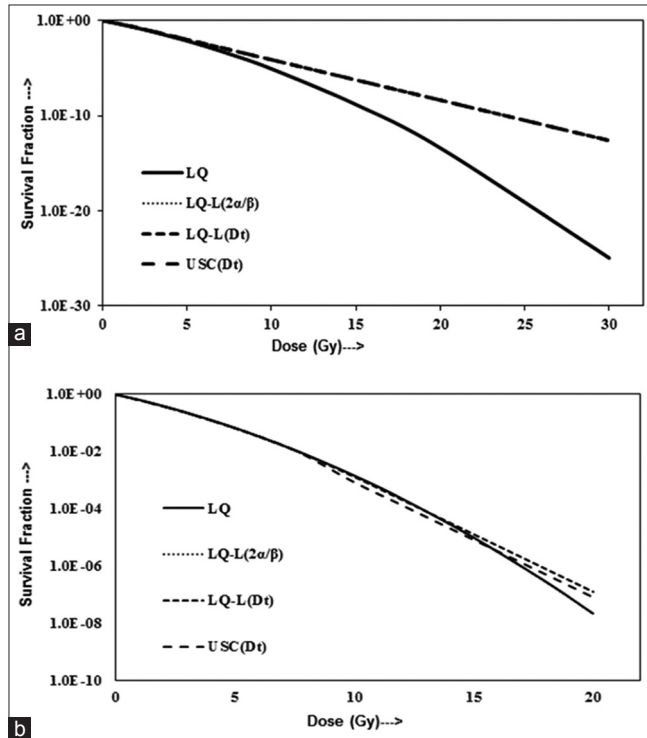


The results of this study demonstrate that applicability of the transition dose  $D_t = 2\alpha/\beta$  is valid only if its value is close to  $D_{t-mt}$ . Astraahan<sup>[29]</sup> discussed that the LQ-L( $D_{t-2\alpha/\beta}$ ) curve using a simplification of the transition dose  $D_t = 2\alpha/\beta$  can only be applied where there is smooth and gradual transition of the LQ curve to asymptotic linear portion.

To evaluate relative difference between the LQ, LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) models for fractionated SBRT, the BED and EQD2

were calculated for the dose scheme used by the RTOG 0813<sup>[46]</sup> protocol from level 1 to level 9 varying from 8 Gy to 12 Gy per fraction delivered in 5 fractions. The values of BED and EQD2 calculated using the LQ, LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) models, for SC and NSC lung cancers, for representative parameters [Table 3], show that for the RTOG 0813<sup>[46]</sup> dose levels, the BED (or EQD2) calculated by the LQ model gives unrealistic dose potency that varied from 1.05 to 1.22 times for SC lung cancer, and from 1.02 to 1.16 times for NSC lung cancers, higher than that calculated by the LQ-L( $D_{t-mt}$ ) model. The BED (or EQD2) of LQ model was higher by 1.1 to 1.44 times for SC and by 1.05 to 1.24 times for NSC lung cancers than that calculated by the USC( $D_{t-mt}$ ) model. Similarly the values of BED (or EQD2) calculated by the LQ-L( $D_{t-mt}$ ) were 1.10–1.18 and 1.03–1.107 times higher than that calculated by the USC( $D_{t-mt}$ ) model for SC and NSC lung cancers, respectively.

It is seen in the Table 4 that the LQ model grossly overestimates the BED (or EQD2) for large dose per fraction treatment, and is likely flawed. The comparison between LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ), shows that the calculated survival fraction and BED (or EQD2), for RTOG 0813 dose scheme, is less sensitive for the USC( $D_{t-mt}$ ) model and does not transition smoothly and gradually from the LQ model to asymptotic linear

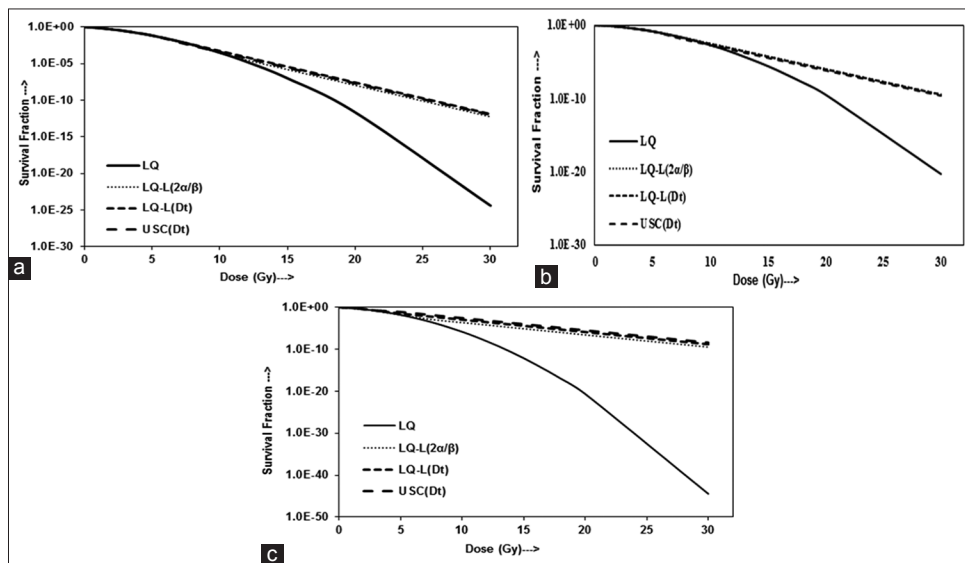


**Figure 5:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for adenocarcinoma lung cancer cell lines data digitized from Carmichael *et al.*'s charts<sup>[44]</sup>

**Table 3: Representative parameters used to plot survival curves in the linear quadratic, linear quadratic-L ( $D_{t-2\alpha/\beta}$ ), linear quadratic-L ( $D_{t-mt}$ ) and universal-survival-curve ( $D_{t-mt}$ ) models and to calculate biologically effective dose and equivalent dose in 2 Gy fractions for RTOG 0813 dose scheme**

Cell lines	$\alpha$ (/Gy)	$\beta$ (/Gy)	$\alpha/\beta$ (Gy)	$D_0$ (Gy)	$\bar{n}$	$D_{t-mt}$ (Gy)
SC	0.47	0.07	6.71	1.05	3.89	5.63
NSC	0.30	0.05	6.00	1.19	5.95	6.60

SC: Small cell lung cancer, NSC: Non-small cell lung cancer

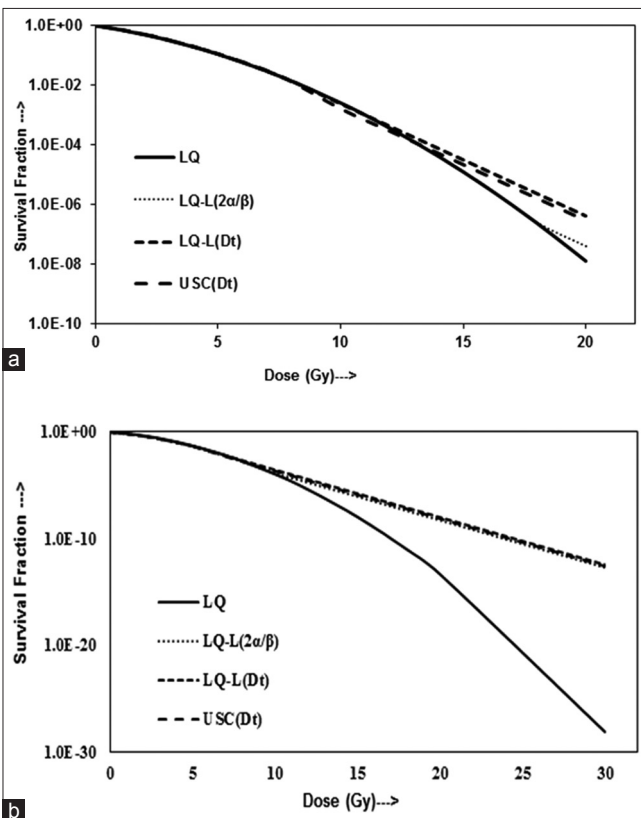


**Figure 6:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for adenosquamous lung cancer cell lines data digitized from Carmichael *et al.*'s charts<sup>[44]</sup>

**Table 4: Biologically effective dose and equivalent dose in 2 Gy fractions calculated for RTOG 0813 dose scheme of lung stereotactic body radiation therapy cases using representative parameters into the linear quadratic, linear quadratic-L ( $D_{t-mt}$ ) and USC ( $D_{t-mt}$ ) models, for small cell and non-small cell lung cancers**

RTOG 0813 dose fractionation scheme		SC lung cancer						NSC lung cancer					
Dose/Fraction	TD	LQ		LQ-L ( $D_{t-mt}$ )		USC ( $D_{t-mt}$ )		LQ		LQ-L ( $D_{t-mt}$ )		USC ( $D_{t-mt}$ )	
		BED	EQD2	BED	EQD2	BED	EQD2	BED	EQD2	BED	EQD2	BED	EQD2
8.0	40.0	87.7	67.6	83.5	64.3	75.8	58.4	93.3	70.0	91.7	68.8	88.9	66.7
8.5	42.5	96.3	74.2	90.2	69.5	80.8	62.3	102.7	77.0	99.7	74.8	95.9	71.9
9.0	45.0	105.4	81.2	96.9	74.6	85.9	66.2	112.5	84.4	107.7	80.8	102.9	77.2
9.5	47.5	114.8	88.4	103.6	79.8	91.0	70.1	122.7	92.0	115.7	86.8	109.9	82.4
10.0	50.0	124.5	95.9	110.3	85.0	96.0	74.0	133.3	100.0	123.7	92.8	116.9	87.7
10.5	52.5	134.7	103.7	117.0	90.1	101.1	77.9	144.4	108.3	131.7	98.8	123.9	92.9
11.0	55.0	145.2	111.8	123.7	95.3	106.2	81.8	155.8	116.9	139.7	104.8	130.9	98.2
11.5	57.5	156.0	120.2	130.4	100.4	111.2	85.7	167.7	125.8	147.7	110.8	137.9	103.4
12.0	60.0	167.3	128.9	137.1	105.6	116.3	89.6	180.0	135.0	155.7	116.8	144.9	108.7

SC: Small cell lung cancer, NSC: Non-small cell lung cancer, LQ: Linear quadratic, BED: Biologically effective dose, EQD2: Equivalent dose in 2 Gy fractions, USC: Universal-survival-curve, TD: Total dose

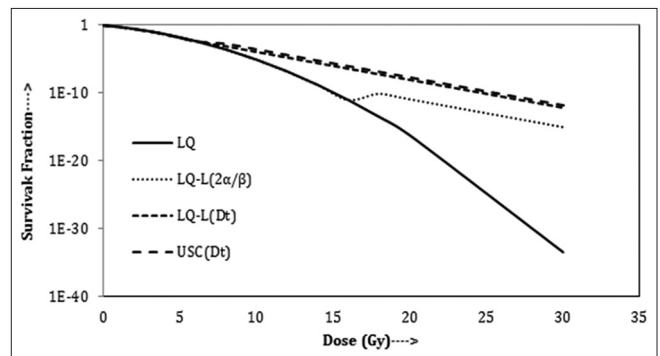


**Figure 7:** Cell survival curves plotted for the linear quadratic, linear quadratic-linear and universal survival curve models for squamous lung cancer cell lines data digitized from Carmichael *et al.*'s charts<sup>[44]</sup>

portion compared to the LQ-L( $D_{t-mt}$ ) model. At the same time the USC( $D_{t-mt}$ ) is unable to address radiobiological issues associated with SBRT treatment.

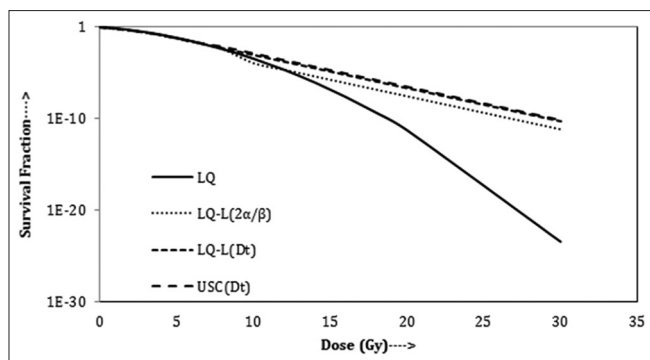
### CONCLUSIONS

The LQ-L( $D_{t-mt}$ ) model provides best fit with smooth and gradual transition of the LQ model to linear portion of the



**Figure 8:** Cell survival curves for SC cells using representative parameters in the linear quadratic, linear quadratic-linear ( $t_{-2\alpha/\beta}$ ), linear quadratic-linear ( $D_{t-mt}$ ) and universal survival curve ( $D_{t-mt}$ ) models

survival curve at transition dose  $D_{t-mt}$ . The  $D_{t-mt}$  describes the dose at which the LQ model loses its validity and final linear portion of the curve begins. The fitting of the experimental dose response data in the range of high doses, used in SRS and SBRT, to the LQ, LQ-L( $D_{t-2\alpha/\beta}$ ), LQ-L( $D_{t-mt}$ ) and USC( $D_{t-mt}$ ) models illustrates that the LQ-L( $D_{t-mt}$ ) model provides the best explanation of the problem. On the other hand, the LQ model overestimates the severity of response at high doses due to continuous bending of the curve, while the LQ-L( $D_{t-2\alpha/\beta}$ ) and USC( $D_{t-mt}$ ) models do not transition smoothly to the linear portion of the curve. Results of this study show that the LQ-L( $D_{t-mt}$ ) model is able to fit wide variety of cell survival data over a very wide range of doses. The transition dose  $D_{t-mt}$  and final slope  $\gamma$ , the  $\log_e$  cell kill per unit dose in the final linear portion of the survival curve, can be calculated using  $D_0$  and  $\bar{n}$  obtained by the best fit exponential regression of experimental or multi-fraction dose response data. Plots of this study show that the LQ-L( $D_{t-mt}$ ) model offers a best description of the cell survival data for SC and NSC cell lines in the high dose region well beyond the shoulder. With the LQ-L( $D_{t-mt}$ ) model, the LQ model retains its all strengths in the low-dose range. The results of this study demonstrate that the LQ-L( $D_{t-mt}$ )



**Figure 9:** Cell survival curves for NSC cells using representative parameters in the linear quadratic, linear quadratic-linear ( $D_{t-2\alpha/\beta}$ ), linear quadratic-linear (Dt-mt) and universal survival curve (Dt-mt) models

would be the greatest clinical tool for intercomparison of conventional and hypofractionated treatment schemes.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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