Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation

Melvin Astrahan[a]

Department of Radiation Oncology, University of Southern California Keck School of Medicine,
1441 Eastlake Avenue, Los Angeles, California 90033

Recent technological advances enable radiation therapy to be delivered in a highly conformal manner to targets located almost anywhere in the body. This capability has renewed the clinical interest in hypofractionation wherein the tumor is delivered a few fractions of very large dose per fraction. Extrapolating clinical experience from conventional regimens to fractions of high dose is important to designing hypofractionated treatments. The concept of biologically effective dose (BED) based on the linear-quadratic (LQ) formulation $e^{-(\alpha D + \beta D^2)}$ is a useful tool for intercomparing conventional fractionations but may be hampered if the value of α/β is dose range dependent and/or when extrapolating to fractions of high dose because the LQ curve bends continuously on the log-linear plot. This does not coincide with what is observed experimentally in many clonogenic cell survival studies at high dose wherein radiation dose-response relationships more closely approximate a straight line. Intercomparison of conventional fractionations with hypofractionated regimens may benefit from BED calculations which instead use a dose range independent linear-quadratic-linear (LQ-L) formulation which better fits the experimental data across a wider range of dose. The dosimetric implications of LQ-L are explored using a simple model which requires only the specification of a dose D_T at which the LQ curve transitions to final linearity and the $\log_e$ cell kill per Gy in the final linear portion of the survival curve at high dose. It is shown that the line tangent to the LQ curve at transition dose D_T can often be used to approximate the final slope of the dose response curve. When $D_T = 2\alpha/\beta$ Gy, the line tangent to the LQ curve at D_T intersects the $e^{-\alpha D}$ and $e^{-\beta D^2}$ curves at dose α/β Gy and also closely fits the linear response in the high dose region of some classic *in vitro* cell survival curves for which the value of α/β is low. It is hypothesized that D_T will increase as the magnitude of α/β increases. Examples are presented illustrating how to recognize LQ-L behavior in multifraction isoeffect studies of late responses such as spinal cord and lung. When planning hypofractionated regimens involving reactions with low α/β, recognizing LQ-L behavior could be important because the dose-response is likely to transition to final linearity within the contemplated range of hypofractional doses. © *2008 American Association of Physicists in Medicine.* [DOI: 10.1118/1.2969065]

Key words: biologically effective dose, BED, linear-quadratic, hypofractionation

I. INTRODUCTION

Recent advances such as stereotactic body radiotherapy (SBRT) enable radiation therapy to be delivered in a highly conformal manner to targets located almost anywhere in the body. This has renewed clinical interest in hypofractionation wherein the target is delivered a few fractions of very large dose per fraction. Hypofractionation is of perpetual interest to the practice of radiation therapy because of its potential to reduce both the logistical and economic costs of therapy compared to conventional treatment regimens. Generally, however, increasing fraction size has been discouraged[1] because when larger fractions are used, late sequelae tend to become more severe compared to conventional regimens, even when acute morbidity and tumor response may have been matched by an appropriate adjustment in total dose. The ability to extrapolate conventional clinical experience for tumor and normal tissues to fractions of high dose will be of great value when contemplating hypofractionated treatments.

Much of our interpretation of tumor and normal tissue response to radiation therapy derives from *in vitro* and *in vivo* survival experiments using clonogenic cells of mammalian and human origin which are exposed to a broad range of radiation dose. At present, the most popular method of fitting a curve to these experimental results is the linear-quadratic (LQ) formula. The LQ model is based upon the assumption that the biological response to radiation can be described by an equation with two principle components, one that is proportional to dose and another that is proportional to the square of the dose. The concept derives from studies in which mitotic death of mammalian cells was found to be strongly associated with asymmetrical exchange-type chromosome aberrations (e.g., dicentric or ring) which require two chromosome breaks.[2]

When the LQ formula is applied to single fraction cell survival curves, the surviving fraction (SF) is commonly expressed as

data from Elkind MM, Sutton H. X-ray damage and recovery in mammalian cells in culture. *Nature* 1959;184:1293–1295
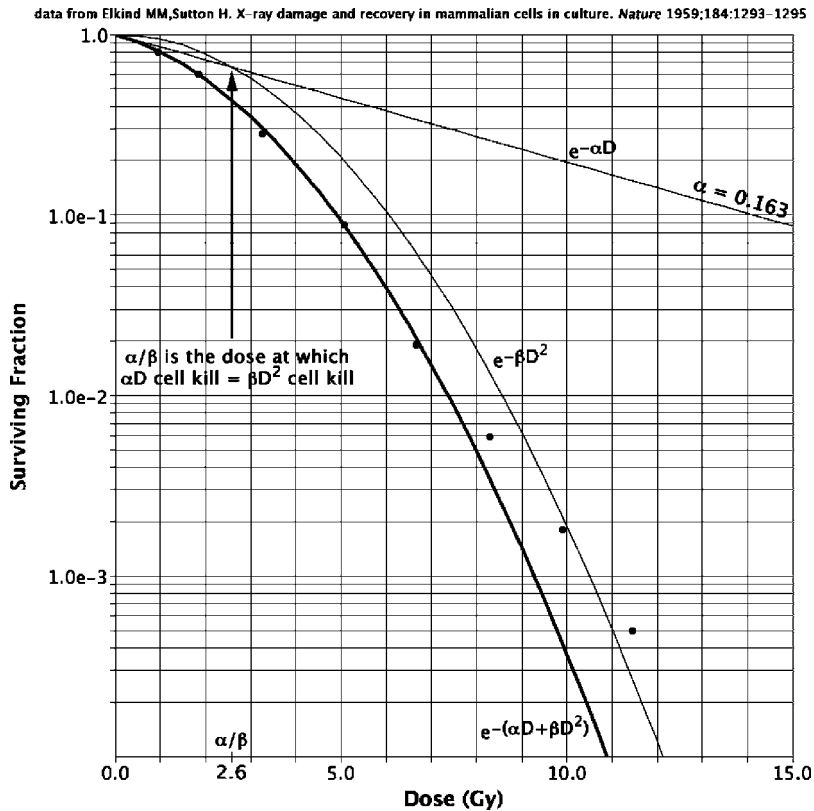

FIG. 1. On the log-linear plot, the LQ curve closely fits these experimental results for Chinese hamster cells in culture up to a dose of 6 Gy, but then continues to bend. The experimental results are observed to become linear at high dose.

$$SF = e^{-(\alpha D + \beta D^2)}, \tag{1}$$

where D is the fraction dose, the constant α is the $\log_e$ cell kill per Gy of the linear component, and β is the $\log_e$ cell kill per Gy^2 of the quadratic component of the survival curve.

This is illustrated in Fig. 1 where Eq. (1) has been applied to survival data for Chinese hamster cells in culture exposed to X-rays taken from an early article by Elkind and Sutton.[3] The survival curve for these cells exhibits a moderately wide initial shoulder. Curves for the individual LQ components $e^{-\alpha D}$ and $e^{-\beta D^2}$ intersect at the dose where the αD and βD^2 components of cell killing are equal. This intersection happens to occur at a dose equal to α/β and is often referred to in the literature simply as α/β with units of Gy. In this work references to the unitless ratio of the magnitudes of the constants α and β will include the identifier "ratio" (e.g., the α/β ratio). When α/β appears alone or accompanied by a unit of dose it will implicitly imply the dose at which the component curves intersect.

The LQ formula is not always compatible with cell survival experiments. For example, in Fig. 2, LQ curves (color dashed lines) have been superimposed on a compilation of survival curves for asynchronous cultures of a number of cell lines of human and rodent origin. These data (black symbols and lines) were digitized from Fig. 3.9A in Hall's radiobiology textbook.[2] Solutions for α and the ratio α/β can be found which allow the LQ equation to closely fit most of the examples for doses up to 6 Gy, but the LQ model is incompatible the two most radioresistant examples, EMT-6 mouse tumor and a glioblastoma of human origin, which are char-

acterized by very broad shoulders. For the glioblastoma data (black squares), α was estimated by setting the ratio of α to β to a very large number (e.g., 100) and then finding the value of α for which the LQ curve passes through the first data point at about 2 Gy with the result $\alpha \approx 0.05$ Gy^{-1}. The red dashed lines are curves for $\alpha = 0.05$ Gy^{-1} and various values of the ratio α/β. There exists no solution for the ratio α/β that allows the LQ formula (1) to adequately fit these data. Although imperfect, the LQ model does closely fit experimental cell survival and multifraction isoeffect results far more often than not and therefore has become a popular method of modeling radiation dose-response.

The concept of biologically effective dose (BED) based on the LQ model[2,4] has provided a fairly reliable tool for intercomparing fractionation regimens *in vivo*[1–8] that employ nominally conventional fraction sizes up to about 6 Gy/fraction. For the calculation of isoeffective relationships the biological effect (E) per fraction (n) of fractional dose (D) can be expressed as $E_n = (\alpha D + \beta D^2)$ and the biologically effective dose per fraction is $BED_n = E_n/\alpha$. It is generally assumed that the fractions are well separated in time so that full repair occurs between fractions and that the biological effect of each fraction is the same. The formula for total BED for n well separated fractions of D per fraction can be written

$$BED = nD + (nD^2/(\alpha/\beta)), \tag{2}$$

where α/β implies the dose at which the LQ components $e^{-\alpha D}$ and $e^{-\beta D^2}$ intersect. It is conventional to express D and

α/β in units of Gy and BED in units of $\mathrm{Gy}_{\alpha/\beta}$ to indicate the reactions to which the result apply.

In addition to being incompatible with the examples of cell survival characterized by broad shoulders in Fig. 2, the fundamental LQ formulation also exhibits additional weaknesses,[9–12] especially when applied to the high dose region of clonogenic cell survival curves. For instance, Garcia et al.[9] recently pointed out that when α/β ratios were determined by fitting the LQ formula to the experimental results of four different cell lines in vitro, the resulting solutions varied significantly as a function of the dose range over which the curve was fit. If the ratio α/β is dose range dependent, then BED calculations will also be dose range dependent because BED is a function of the dose α/β Gy. This complicates use of the BED concept for intercomparing dose fractionation regimens. To keep BED calculations simple, a dose-range independent approximation for the dose α/β Gy is desirable.

Another characteristic of the formulation of Eq. (1) is that the resulting dose-response curve bends continuously on the log-linear plot (LLP). This does not coincide with what is observed experimentally in many clonogenic cell survival studies where the dose-response relationships exhibit an exponential decrease of survival at high dose which more closely approximate a straight line on the LLP.[2,3,13–15] Therefore, in the example illustrated in Fig. 1, the LQ formulation overestimates the magnitude of cell kill, or, equivalently, underestimates the surviving fraction for doses greater than 6 Gy. Should in vivo dose-response relationships behave similarly, then the LQ formulation will likewise overestimate in vivo response and thus underestimate the dose required to achieve a desired response for fractions of high dose.

These weaknesses of the LQ model could affect the accuracy of BED calculations if the reactions of tumor, normal tissues, or anatomic organs mimic the dose-response characteristics observed for cell survival studies.

To better address high dose per fraction regimens Guerrero and Li[10] proposed a modification to the LQ model which provided a better fit at high doses. Their model was noted by Carlone et al.[14] to exhibit linear-quadratic-linear (LQ-L) behavior. Wang et al.[11] recently presented a "generalized LQ (gLQ)" formula which also exhibits linear-quadratic-linear behavior. The formulas employed in these works attempt to modify the LQ model from a partially mechanistic perspective and are fairly complex. Park et al.[12] recently proposed a bipartite "universal survival curve" hybrid of the LQ and the historic multi-target (MT) model[13] in order to better fit cell survival experiments. In their implementation the LQ model switches to the MT model at a specific transition dose which they coined as D_T. An inconvenience of this approach is that the parameters used by the MT model (n, D_q, and D_0) are determined by extrapolating the final linear portion of the survival curve back to the y axis intercept while the range dependent LQ terms α and β are determined by fitting the LQ formula to some specified range of the experimental data. In order to smoothly fit their experimental data Park et al.[12] solved for β in terms of the other variables and then
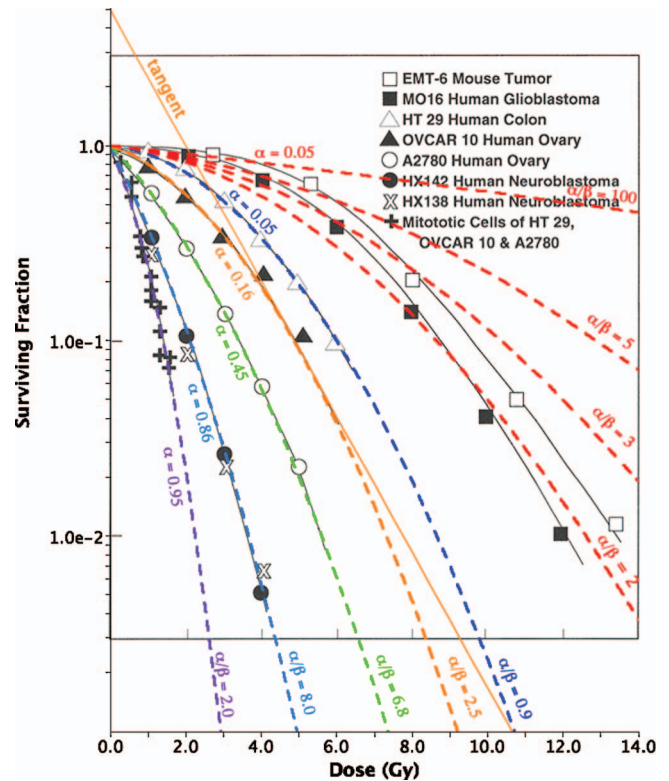

FIG. 2. The LQ formula does not adequately model all cell survival experiments. Here the LQ model has been applied to a compilation of survival curves for asynchronous cultures of a number of cell lines of human and rodent origin digitized from Fig. 3.9A in Hall's[2] textbook. The LQ model is not compatible with the radioresistant examples that exhibit very broad shoulders. See text for further explanation.

solved D_T as a function of α, D_q, and D_0. They demonstrated the ability of their model to fit only a single example of clonogenic cell survival in vitro for a cell line with D_T of about 6 Gy. One can achieve the same type of LQ-L fit to experimental data more efficiently by eliminating the MT formalism and simply specifying the $\log_e$ cell kill per Gy in the final linear portion of the survival curve and a dose D_T at which it begins. This generalization eliminates having to solve n or D_q or β and makes it easier to compute isoBED curves and identify LQ-L dose-response behavior in situations where cell survival curves are not applicable such as the late reactions of spinal cord for which only the ratio α/β can be derived from isoeffect data.

Many extensions to the basic LQ formulation have been developed in an attempt to account for temporal phenomena such as repair of sublethal damage and repopulation which can occur during lengthy fractionated regimens.[2,5,6,10,11,14] For hypofractionated SBRT repopulation will likely not be an issue. Nevertheless, the same methods developed to address these time related issues could be applied in an identical manner to the model developed here.

II. METHODS AND MATERIALS

In this work a more efficient form of the bipartite method proposed by Park et al.[12] is employed to model LQ-L dose-response. If ever used clinically, the herein proposed LQ-L

notation should include subscripts for the dose α/β and the dose D_T at which the curve becomes linear, perhaps in the form $LQ_{\alpha/\beta}$-L_{D_T}. For example, LQ_3-L_6 would describe a model which transitions from LQ with $\alpha/\beta = 3$ Gy to a linear tail for fraction doses greater than 6 Gy.

To transition to an exponential decrease of survival at high dose the LQ model for single fraction survival can be extended to a bipartite form:

$$SF = e^{-(\alpha D + \beta D^2)} \quad \text{for } D < D_T \tag{3a}$$

and

$$SF = e^{-(\alpha D_T + \beta D_T^2 + \gamma(D - D_T))} \quad \text{for } D \geq D_T. \tag{3b}$$

For plotting on the LLP, this can equivalently be expressed as

$$\log_e(SF) = -(\alpha D + \beta D^2) \quad \text{for } D < D_T \tag{4a}$$

and

$$\log_e(SF) = -(\alpha D_T + \beta D_T^2 + \gamma(D - D_T)) \quad \text{for } D \geq D_T \tag{4b}$$

where γ is the $\log_e$ cell kill per Gy in the final linear portion of the survival curve at high dose. The term γ is reminiscent of D_0, the dose that reduces survival by $1/e$ in the final linear portion of the MT survival model, but is more in keeping with the notation and conventions of the LQ model.

For the bipartite model, the formulation for BED per fraction becomes:

$$BED_n = D + [D^2/(\alpha/\beta)] \quad \text{for } D < D_T \tag{5}$$

and

$$BED_n = D_T + [D_T^2/(\alpha/\beta)] + [(\gamma/\alpha)(D - D_T)] \quad \text{for } D \geq D_T, \tag{6}$$

For intercomparing fractionation regimens, the bipartite form of the BED formula above has the minor disadvantage in that it requires the ratio γ/α in addition to the dose α/β. Implementation of BED calculations would be simpler if an approximation of the ratio γ/α could be derived from the dose α/β.

Let us hypothesize that for those dose-response studies which the LQ formula fits closely and which smoothly transition to linearity there will exist some dose D_T at which γ can be approximated as the slope of the line tangent to the LQ curve at dose D_T. The concept is illustrated by the solid orange line in Fig. 2 which is the tangent to the LQ solution (dashed orange line) for the human ovary cell line (black triangle symbols) assuming $D_T = 5$ Gy. The slope of the tangent can be calculated from the derivative as

$$\gamma = (\alpha + 2\beta D_T) = \alpha(1 + (2D_T/(\alpha/\beta))). \tag{7}$$

From the tangent at D_T, γ/α is

$$\gamma/\alpha = 1 + [2D_T/(\alpha/\beta)]. \tag{8}$$

Assuming that a dose-range independent approximation for α/β is available, substituting Eq. (8) into Eq. (6) allows

BED to be estimated by specifying just one additional term, the transition dose D_T. This is simpler than the method proposed by Park et al.,[12] which required several terms.

Software was developed which allowed interactive manipulation of the α, α/β, and D_T parameters of the LQ-L model for rapid curve fitting by inspection to digitally scanned images of published dose-response and multifraction isoeffect plots.

III. RESULTS

In Fig. 3, the LQ-L model has been fit by interactive inspection to examples of published cell survival obtained *in vitro* using colony forming assays and *in vivo* by histological examination. Figure 3(a) plots surviving fraction for the same classic Chinese hamster data as in Fig. 1. When $\alpha = 0.163$ Gy^{-1} and $\alpha/\beta = 2.6$ Gy, the LQ curve in Fig. 1 fits the experimental results closely up to about 6 Gy. In Fig. 3(a) the tangent (blue line) to the LQ curve at $D_T = 2\alpha/\beta$ Gy (5.2 Gy) intersects the $e^{-\alpha D}$ and $e^{-\beta D^2}$ curves (green lines) at dose α/β Gy and also closely fits the final linear portion of the experimental results. The resulting $LQ_{2.6}$-$L_{5.2}$ curve is plotted in red.

In Fig. 3(b) the LQ-L model (red dashed line) has been superimposed onto a classic survival curve (black) for human HeLa cells in culture that was digitized from a figure in Hall's textbook,[2] which was reprinted from Ref. 15. The survival curve for these cells has a small initial shoulder. For $\alpha/\beta = 0.9$ Gy and again with $D_T = 2\alpha/\beta$ Gy (1.8 Gy) the LQ-L model superimposes almost perfectly over the black line drawn by Puck and Markus[15] across the entire experimental dose range. The component curves for $e^{-\alpha D}$ and $e^{-\beta D^2}$ are plotted in green. The tangent to the LQ-L curve at D_T is plotted in blue. The three curves intersect at dose α/β Gy. For historical interest, values are also shown for the MT model extrapolation number (n), quasithreshold dose (D_q), and final slope (D_0) that resulted from the LQ-L curve fit.

In Fig. 3(c) the standard LQ formula (1), with $\alpha = 0.208$ Gy^{-1} and $\alpha/\beta = 12.0$ Gy, has been superimposed onto *in vivo* survival data for mouse testes stem cells that were digitized from another figure in Hall's textbook[2] which was, in turn, reprinted from Ref. 16. In the dose range studied it is not clear that these results ever achieve final linearity because the LQ curve (dashed red line) appears to fit the data in the high dose region just as well as the black line originally drawn by Thames and Withers.[16] If survival curves for cells with high α/β follow a pattern similar to the examples for low α/β in Figs. 3(a) and 3(b), then one can hypothesize that the LLP linear region for these cells will begin at a dose of about 24 Gy (i.e., $\approx 2\alpha/\beta$), which is well beyond the range of these experimental data.

In Fig. 3(d) an LQ-L model with $\alpha = 0.045$ Gy^{-1}, $\alpha/\beta = 1.6$ Gy, $D_T = 11.0$ Gy, and γ the tangent at D_T has been superimposed onto survival data for $C3H/10T^{1/2}$ cells in culture that were digitized from Chart 2 in Ref. 17. $C3H/10T^{1/2}$ is a mouse embryo-derived cell line which is fibroblastic in nature and which is often used to study oncogenic transformation. The survival curve is characterized by a very broad
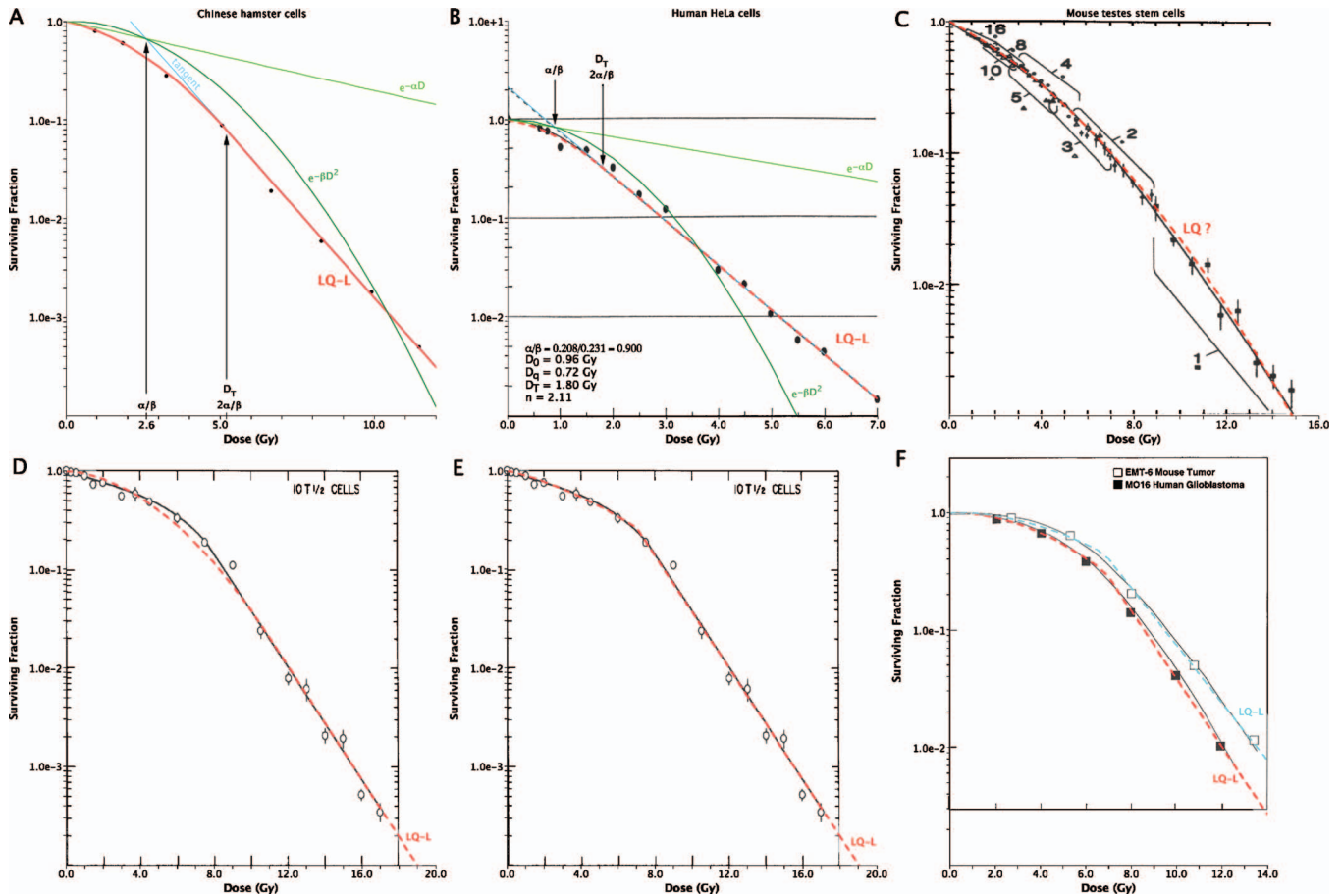
FIG. 3. (a) The line tangent to the curve at $D_T=2\alpha/\beta$ Gy fits the final linear portion of the experimental results for the Chinese hamster cells in culture shown in Fig. 1. (b) An LQ-L curve (red dashed line) with $D_T=2\alpha/\beta$ Gy superimposes almost perfectly over the curve originally drawn by Puck and Markus (Ref. 15) for HeLa cells in culture. (c) An LQ curve (red dashed line) superimposed over *in vivo* survival data for mouse testes stem cells from Ref. 16. The numbers on the curve refer to the number of fractions used to reconstruct that portion of the curve from large doses delivered as multiple small fractions. In the dose range studied one can not determine if the response has yet become linear at high dose. (d) An LQ-L curve (red dashed line) with γ constrained to be the tangent at D_T superimposed over survival data for mouse C3H/10T1/2 cells in culture from Han Ref. 17. These cells exhibit an almost bilinear response. (e) The LQ-L model (red dashed line) can better fit these data when γ and D_T are unconstrained. (f) The unconstrained LQ-L model (red and blue dashed lines) can also adequately fit the radioresistant examples from Fig. 2.

shoulder followed by a sharp bend at about 7 Gy. In fact, the results appear more bilinear on the LLP rather than linear-quadratic.

The LQ-L model can also fit survival data such as these by explicitly specifying solutions for D_T and γ. For instance, in Fig. 3(e) the LQ-L model with $\alpha=0.11$ Gy^{-1}, $\alpha/\beta=9.6$ Gy, $D_T=7.0$ Gy, and $\gamma=0.654$ Gy^{-1} better fits the same survival data as Fig. 3(d). An alternative approach that eliminates the need to explicitly solve for γ is to multiply the slope of the tangent at D_T by a constant k in which case Eq. (8) becomes

$$\gamma/\alpha = k(1 + [2D_T/(\alpha/\beta)]). \qquad (9)$$

In Fig. 3(e) the same LQ-L curve results when one uses the tangent at D_T and $k=2.42$. The advantage of Eq. (9) is that it makes BED calculations simpler to implement.

In Fig. 3(f) the LQ-L model is shown to be able to better adapt to the radioresistant examples of Fig. 2 than was the LQ model. The LQ-L solution used to calculate the red curve is $\alpha=0.0005$ Gy^{-1}, $\alpha/\beta=0.02$ Gy, D_T

$=6.9$ Gy, $\gamma=0.667$ Gy^{-1} (or $k=1.93$) and for the blue curve $\alpha=0.0001$ Gy^{-1}, $\alpha/\beta=0.0058$ Gy, $D_T=6.8$ Gy, $\gamma=0.565$ Gy^{-1} (or $k=2.41$).

In Fig. 4, LQ-L solutions are superimposed over *in vitro* survival data for DU145 and CP3 cells that were recently published as Fig. 1 in Garcia *et al.*[9] Both cell lines are of human prostate origin. DU145 was isolated from a brain metastasis by Stone *et al.*[18] Leith *et al.*[19] studied this cell line *in vitro* up to doses of 6 Gy and reported radiation survival parameter values of $\alpha=0.155$ Gy^{-1} and $\alpha/\beta=2.97$ Gy for the linear-quadratic model. Garcia *et al.*[9] demonstrated a range dependence to the LQ fit for these cell lines. To make their results more meaningful, they elected to divide the dose range in their study into regions of low-dose (LR), linear-quadratic (LQR), and high dose (HR). In Fig. 4(a) the blue dashed line is the best LQ-L fit to the DU145 data that was achievable by inspection with the constraint that the value of α/β has somehow been determined from a previous study (e.g., Ref. 19) and must be exactly equal to 3 Gy, and then
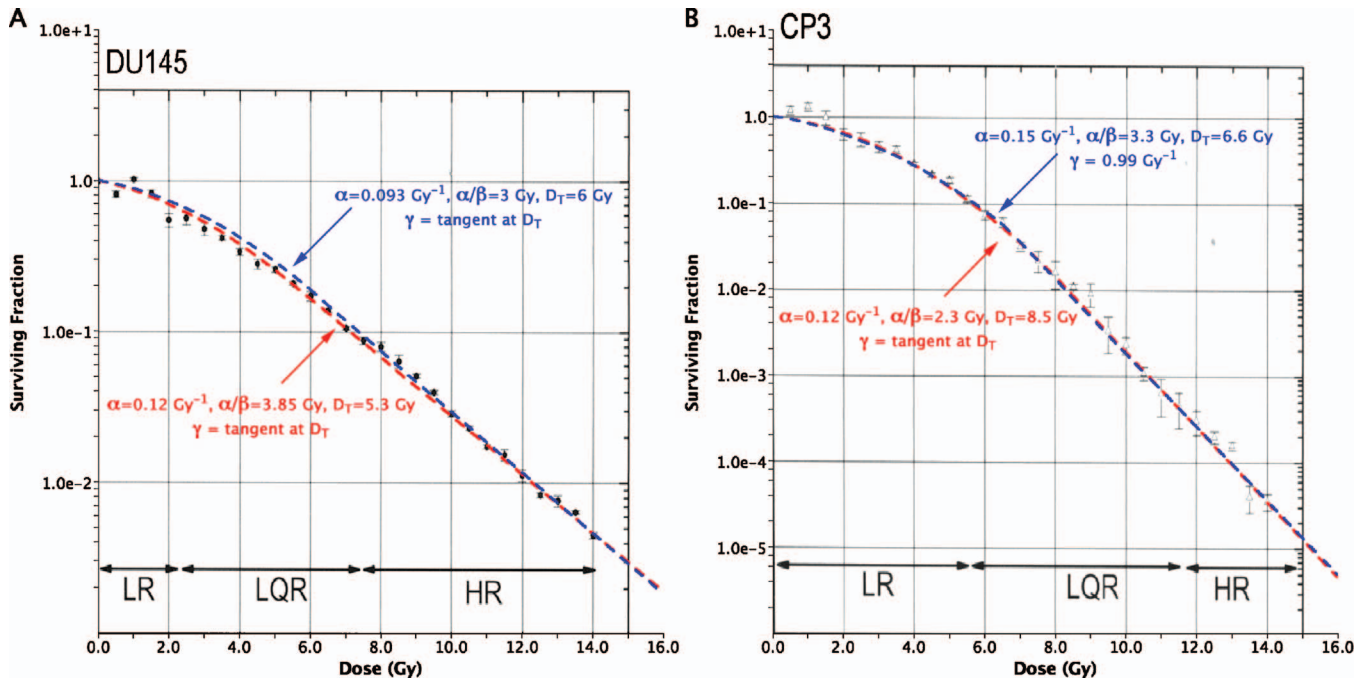
FIG. 4. Comparison of LQ-L models superimposed over recently published (Ref. 9) survival curves for two human prostate carcinoma cell lines *in vitro*. (a) The blue dashed line is the best LQ-L fit achievable by inspection with the triple constraints that $\alpha/\beta=3$ Gy, $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T. The red dashed line only constraints γ to be the tangent at D_T. (b) The blue dashed line is an LQ-L solution with the single constraint that $D_T=2\alpha/\beta$ Gy, the values of α/β and γ are unconstrained. The red dashed line is an LQ-L solution with the single simplification that γ be the tangent at D_T. The two solutions yield similar, but not identical results when used to intercompare BED and fractionation regimens.

assuming the LQ-L approximations of $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T. The red dashed line only constrains γ to be the tangent at D_T; the values of α/β and D_T are allowed to adapt to better fit the data. In Fig. 4(b), the blue dashed line is an LQ-L solution for the CP3 data with the single constraint that $D_T=2\alpha/\beta$ Gy; the values of α/β and γ were unconstrained. The red dashed line is a solution with the single constraint that γ be the tangent at D_T. The two curves are almost indistinguishable across the experimental data range.

The point here is that the LQ-L model is flexible enough to closely fit the entire range of experimental data, even if various simplifying assumptions, approximations, constraints, or combinations thereof are enforced. The solution

for α/β will be dose range independent so that BED for a particular reaction can be intercompared across the entire dose range. The different simplifications, however, generate slightly different solutions for α and hence the solution for α/β will vary as well. This could affect BED calculations because the BED formula requires the α/β term. The results of Fig. 4 suggest that variations in α/β of ±1 Gy might be expected depending upon which, if any, simplifying assumptions were used to fit the data.

Calculations were performed to explore how approximating the value of α/β would affect the intercomparison of fractionation regimens. Table I compares fractionations calculated to be the BED equivalent of 30 fractions of 200 cGy/fraction for α/β in the range 2 to 11 Gy using the

TABLE I. Fractionation regimens calculated to have BED equivalent to a standard course of 30×200 cGy/fraction according to the LQ and LQ-L models for α/β in the range 2–11 Gy and assuming $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T.

		LQ					LQ-L		
α/β (Gy)	$BED_{\alpha/\beta}$	20 Fractions of (cGy)	10 Fractions of (cGy)	5 Fractions of (cGy)	3 Fractions of (cGy)	2 Fractions of (cGy)	5 Fractions of (cGy)	3 Fractions of (cGy)	2 Fractions of (cGy)
2	120.0 Gy_2	261	400	600	800	1000	640	960	1360
3	100.0 Gy_3	265	418	639	861	1084	640	907	1240
4	90.0 Gy_4	269	432	672	914	1156	672	920	1220
9	73.3 Gy_9	280	479	784	1100	1421	784	1100	1421
10	72.0 Gy_{10}	281	485	800	1128	1462	800	1128	1462
11	70.9 Gy_{11}	282	490	815	1154	1500	815	1154	1500

TABLE II. Data for α/β in the range 9 to 11 Gy from Table I normalized to the results for $\alpha/\beta=10$ Gy.

α/β (Gy)	$BED_{\alpha/\beta}$	LQ					LQ-L		
		20 Fractions	10 Fractions	5 Fractions	3 Fractions	2 Fractions	5 Fractions	3 Fractions	2 Fractions
9	73.3 Gy$_9$	0.996	0.99	0.98	0.98	0.97	0.98	0.98	0.97
10	72.0 Gy$_{10}$	1	1	1	1	1	1	1	1
11	70.9 Gy$_{11}$	1.003	1.01	1.02	1.02	1.03	1.02	1.02	1.03

LQ model and the LQ-L model with the approximations $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T. Note that the results calculated using the LQ-L model for α/β in the range 9 to 11 Gy are identical to the LQ results because under the assumption $D_T=2\alpha/\beta$ Gy, the two models do not differ until fraction doses exceed 18 to 22 Gy. In Tables II and III the results of Table I have been normalized to the dose per fraction calculated for $\alpha/\beta=10$ Gy and 3 Gy respectively.

In Table II we see that for high α/β in the range 10 ± 1 Gy, all results differ by less than $\pm3\%$ from the dose per fraction for $\alpha/\beta=10$ Gy. These results suggest that approximating α/β to within about ±1 Gy may be sufficient for clinical calculations involving high α/β. In Table III, for lower α/β in the range 3 ± 1 Gy, the differences are a little greater than were seen in Table II. For nominally conventional regimens employing more than 5 fractions, approximating α/β to within about ±1 Gy may be sufficient for clinical calculations. The main point here is that extrapolating clinical experience accumulated with conventional regimens to hypofractionation will probably have its greatest uncertainty when the magnitude of α/β is low.

In Fig. 5 isoBED curves calculated using the LQ (colored solid lines) and LQ-L (colored dashed line) models are superimposed onto isoeffect data and curves (black symbols and lines) for early and late effects in various organs of laboratory animals digitized from Fig. 1 in Ref. 1. In the original figure late effects were plotted with solid black lines, acute effects with dashed black lines. These data are also reproduced as Fig. 22.7 in Hall's textbook.[2] The biological endpoints studied were not specified. The figure was originally intended to illustrate that isodoses for late effects increase more rapidly with decrease in dose per fraction than for acute effects. The solutions for α/β which resulted in the closest isoBED fit (by inspection) to the experimental results are displayed in matching color to the left of each LQ curve.

Observe that all of the isoBED curves calculated using the LQ model smoothly and continuously curve downward with increase in dose per fraction.

Among the tissues and organs with low α/β, late effects for spinal cord and kidney do not exhibit LQ-L behavior in this experimental dose range because the isoeffect data continues to bend downward as dose increases, even above $2\alpha/\beta$ Gy. However, for lung, the experimental data does not continuously bend downwards with increasing dose and can be fit by an LQ-L model (red dashed line) with $\alpha/\beta=2.4$ Gy, $D_T=4.2$ Gy ($\approx 2\alpha/\beta$), and γ estimated as the tangent at D_T. The dose range of the data for the other late effects is not wide enough enough to determine if LQ-L behavior applies.

LQ-L behavior will be recognizable on log-log plots of isoeffect studies by an inflection point in the isoeffect curve as illustrated for the lung data. LQ-L behavior for the acute reactions in this figure would only be noticeable if the transition to linearity began within the plotted dose range. For acute effects with higher values of α/β (e.g., ≈ 10 Gy) the data are all adequately fit by the LQ model for fraction doses up to 10 Gy; thus, if any of these acute reactions are LQ-L, the transition to linearity must occur at doses >10 Gy/fraction.

In Figs. 6(a) and 6(b) the reciprocal of the total dose required to produce a given biological effect is plotted as a function of the dose per fraction which was delivered as multiple equal fractions. Douglas and Fowler[20] introduced this method to estimate the ratio α/β from the slope and ordinate intercept of the best fit line to the isoeffect data.

The data in Fig. 6(a) for an acute skin reaction in mice were digitized from Fig. 9 in Ref. 20. The hollow and solid diamond symbols were used to denote experiments performed with and without anesthesia. A subset of these data

TABLE III. Data for α/β in the range 2 to 4 Gy from Table I normalized to the results for $\alpha/\beta=3$ Gy.

α/β (Gy)	$BED_{\alpha/\beta}$	LQ					LQ-L		
		20 Fractions	10 Fractions	5 Fractions	3 Fractions	2 Fractions	5 Fractions	3 Fractions	2 Fractions
2	120.0 Gy$_2$	0.98	0.96	0.94	0.93	0.92	1.00	1.06	1.10
3	100.0 Gy$_3$	1	1	1	1	1	1	1	1
4	90.0 Gy$_4$	1.01	1.03	1.05	1.06	1.07	1.05	1.01	0.98

are also reproduced as Fig. 18.26 in Hall's textbook.[2] An isoBED curve calculated using the LQ formula (solid red line) for $\alpha/\beta=10.2$ Gy appears as a straight line on this plot. An isoBED curve calculated using the LQ-L model (dashed red line) for $\alpha/\beta=10.2$ Gy and assuming $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T bends at doses greater than D_T. For doses above 15 Gy/fraction the experimental results are inadequate to confirm LQ behavior or to distinguish between the LQ and LQ-L models. For instance, in the limited range 20 to 25 Gy/fraction, the ordinate values of the 7 data points are inexplicably linearly decreasing with increasing dose per fraction.

In Fig. 5, the LQ formula was observed to closely fit the isoeffect data of a late reaction of mouse spinal cord for fractions up to about 10 Gy. In Fig. 6(b), the reciprocal of the isoeffect dose for three types of spinal cord damage in rats, digitized from Fig. 6.4 in Ref. 21, are plotted out to 20 Gy. The black lines are from the original figure and represent linear fits by regression analysis. The linearity of the cervical white matter necrosis (solid black triangles) data on this plot demonstrates LQ behavior for that syndrome across the entire dose range. The data for cervical vascular damage (hollow triangles), however, exhibit the type of bending that is indicative of LQ-L behavior. An isoBED curve calculated using the LQ-L model (red dashed line) with $\alpha/\beta=1.5$ Gy, $D_T=10.5$ Gy, and γ the tangent at D_T appears to fit the cervical vascular damage data better than a straight line.

Now consider the hypothetical situation in which a tumor with $\alpha/\beta=10$ Gy and its surrounding tissues or organs with $\alpha/\beta=3$ Gy are homogeneously irradiated. When considering a hypofractionated regimen one could opt to maintain equivalent tumor control, or to maintain equivalent late sequelae. In Fig. 7 BED is plotted for late reactions as a function of constant acute effect to the tumor of 72 Gy$_{10}$ and for

acute reactions to the tumor as a function of constant late reactions of 100 Gy$_3$. Increasing BED presumably means increasingly severe late reactions and increasing probability of tumor control.

The LQ model (dashed lines) predicts that for constant tumor control the severity of late reactions progressively increases as the number of fractions decreases and the dose per fraction increases. Conversely, for constant late reactions, the probability of tumor control increases as the number of fractions increases. If late effects are LQ and only the tumor reactions are LQ-L with the approximations $D_T \approx 2\alpha/\beta$ Gy (i.e., $\approx$20 Gy) and γ the tangent at D_T, the results are virtually identical to the LQ curves (dashed lines). This occurs because all of the calculated fraction doses fall below 20 Gy in this study except for a regimen consisting of a single fraction, and even in that case the calculated dose is close to 20 Gy.

However, under the specific assumptions that both the tumor response and late effects happen to exhibit LQ-L behavior (solid line) with $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T, the severity of late sequelae for constant tumor control passes through a maximum at 5 fractions and then decreases as the number of fractions decreases. The calculated dose/fraction that yield constant acute BED=72 Gy$_{10}$ in this peak region are also shown. There is an equivalent converse behavior for constant late reactions. These results must be considered only a demonstration of principle and applicable only to the underlying assumptions. They should not be applied to any clinical situation.

IV. DISCUSSION

One limitation of the conventional LQ formulation is that it may not properly model the exponential decrease of sur-
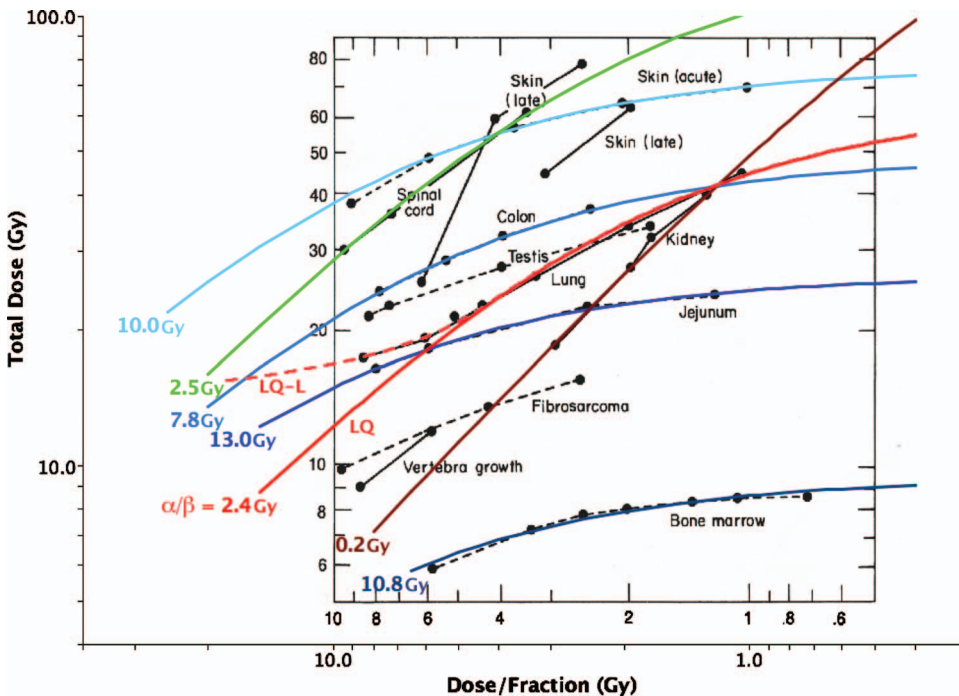

FIG. 5. IsoBED curves calculated using the LQ model (solid lines, various colors) are superimposed onto isoeffect data (black color) digitized from Fig. 1 in Ref. 1 for early and late effects in various organs and tissues of laboratory animals. The values for α/β used in the present modeling are displayed in matching color to the left of each curve. The LQ-L model (dashed red line) with $D_T=4.2$ Gy ($\approx 2\alpha/\beta$) and γ the tangent at D_T appears to fit the isoeffect data for lung better than does the LQ model (solid red line).
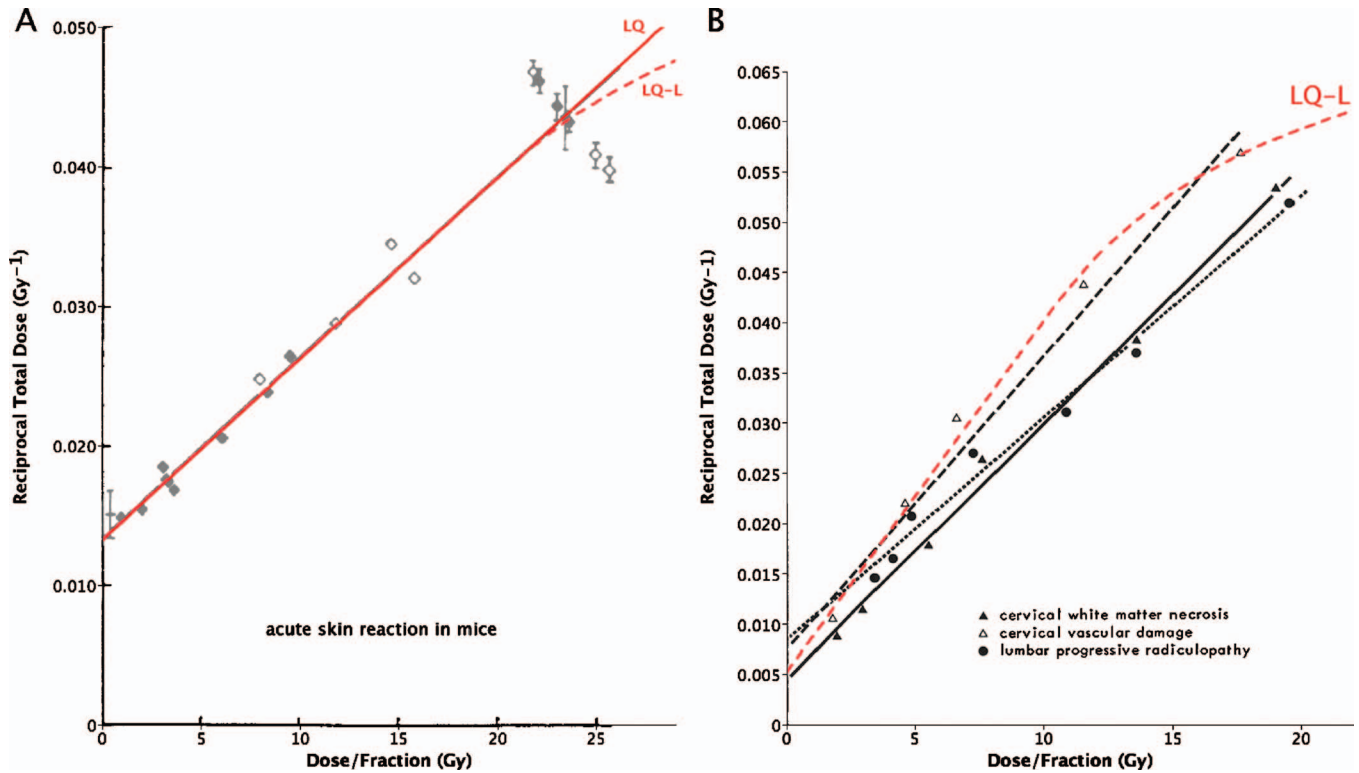
FIG. 6. In these figures the reciprocal of the total dose required to produce a given effect is plotted as a function of the dose per fraction which was delivered as multiple equal fractions. The value of α/β can be estimated from the slope and ordinate intercept of the curve (Ref. 20). (a) These data for an acute skin reaction in mice (gray symbols) were digitized from Fig. 9 in Ref. 20. An isoBED curve calculated using the LQ formula (solid red line) with α/β =10.2 Gy appears as a straight line on this type of plot. An isoBED curve calculated using the LQ-L model (dashed red line) with α/β=10.2 Gy, D_T =$2\alpha/\beta$ Gy, and γ the tangent at D_T bends at doses greater than D_T. The data above 15 Gy are inadequate to differentiate between the LQ and LQ-L models. (b) These data for three types of spinal cord damage in rats were digitized from Fig. 6.4 in Ref. 21. The black lines are from the original figure and represent linear fits by regression analysis. The data for cervical white matter necrosis (solid black triangles) are very linear across the entire dose range, which indicates LQ behavior for that syndrome. The data for cervical vascular damage (hollow triangles) exhibit the type of curvature that is indicative of LQ-L behavior. The red dashed line is an isoBED curve calculated using the LQ-L model with α/β=1.5 Gy, D_T=10.5 Gy, and γ the tangent at D_T.

vival with dose that is often observed at high dose in cell survival studies. When cell kill is the endpoint, the standard LQ model can overestimate the severity of response at high dose because the curve continues to bend. As a result, cell survival will be greater than anticipated and calculations will underestimate the dose required to match the biological effect of conventional fractionation. LQ-L curve fitting models are a simple remedy to this problem.

Garcia *et al.*[9] demonstrated that α/β calculated for various cell lines *in vitro* varied widely depending on the dose range to which the LQ model was fit. LQ-L models eliminate the dose range ambiguity of α/β by requiring the model to fit the entire experimental range of dose. This enforces a dose range independent approximation for α/β which in turn allows for dose range independent intercomparison of fractionation regimens using the BED concept. One does need to be consistent, however, if simplifications to the LQ-L model are assumed (e.g., γ being the tangent at D_T).

The LQ-L model described in this work may also be useful for fitting and interpreting the survival curves of some atypical and radioresistant cell lines. In Fig. 3(e) response appears to become linear on the LLP above 7 Gy. Below 7 Gy, the LQ-L fit yields an α to β ratio of about 10. Lethality across the entire dose range therefore appears to be domi-

nated by events that are exponentially proportional to dose rather than dose squared. In Fig. 3(f), on the other hand, the common features of fitting LQ-L to the two examples of radioresistant cells were that the resulting solutions for the α terms yielded very small numbers, α/β ratios $\ll 1$, and response again appears to possibly become linear on the LLP beyond 7 Gy. When the ratio of α to β is much less than 1 the quadratic term of the LQ formula dominates, which suggests that the mechanism of cell killing for these cells at doses below 7 Gy is associated with a pair of events. The original curves drawn to fit these data assumed smooth curvature, but it is at least a possibility that the response more abruptly transitions to linearity at about 7 Gy. An abrupt transition to steeper linearity might indicate that some repair functionality of these cell lines becomes overwhelmed at about 7 Gy.

When D_T=$2\alpha/\beta$ Gy, the line tangent to the curve at D_T intersects the curves of the individual components $e^{-\alpha D}$ and $e^{-\beta D^2}$ at α/β Gy, the dose at which the linear and quadratic components of cell kill are equal, and also approximates the final linear response of some cell lines. It is intriguing to speculate that that this might be related to some underlying biological mechanism. It remains to be determined, however,
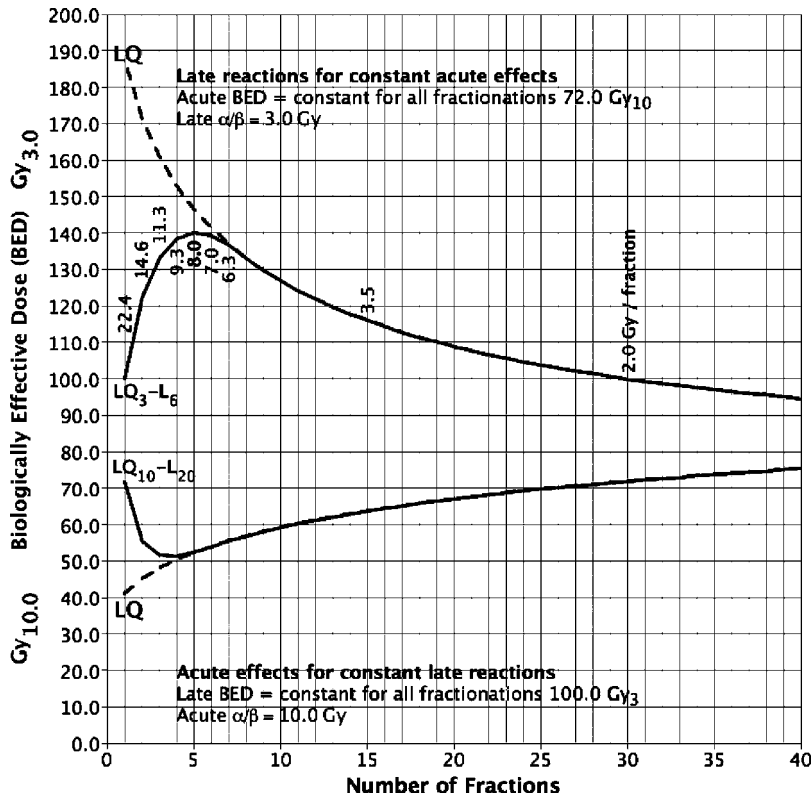
FIG. 7. A hypothetical study of low α/β reactions (e.g., late effects) as a function of constant high α/β reactions (e.g., acute or tumor response) and high α/β reactions as a function of constant low α/β effects, assuming that both low and high α/β reactions exhibit LQ-L behavior with $D_T=2\alpha/\beta$ Gy and γ the tangent at D_T.

how widely the simplifying approximations involving γ being the tangent at D_T and $D_T \approx 2\alpha/\beta$ Gy that were used to explore some of the implications of LQ-L in this work can be applied. For instance, the LQ-L model was able to adequately fit the atypical survival data in Figs. 3(d)–3(f) with which the LQ model is incompatible, but only when all of the simplifying approximations were removed, i.e., both γ and D_T had to be explicitly provided, they could not be estimated from other characteristics of the data. It may be that these simplifications are only applicable to those reactions for which the transition from linear-quadratic to linear is smooth and gradual as seen in Figs. 3(a), 3(b), and 4. Additional research will be required to determine to what extent these simplifications can be applied to the clinic.

As the dose α/β increases, one can hypothesize, however, that D_T will increase proportionally as well. For instance, if $\alpha/\beta=10$ Gy and $D_T \approx 2\alpha/\beta$ Gy, then doses may have to exceed about 20 Gy before the linear portion of the survival curve (on the LLP) begins and the standard LQ model begins to fail. This was illustrated in Figs. 3(c), 5, and 6. Few dose response studies in the literature extend measurements beyond 20 Gy. To support the current resurgence of interest in hypofractionation, it will be of value to extend experimental measurements to doses well beyond $2\alpha/\beta$ Gy for the reaction of interest in order to ascertain if dose response ever becomes linear at hypofraction doses. An interesting implication of $D_T \approx 2\alpha/\beta$ Gy, if applicable, is that Eq. (8) could be simplified by the approximation $\gamma/\alpha \approx 5$.

In regards to late sequelae of irradiation, organ function is presumably related more to the proportion of functional cells remaining in an irradiated organ than to the proportion of

clonogenic cells.[2] Therefore, the ratio α/β for normal tissues and organs is often inferred from the type of multifraction isoeffect experiments[1,2,20,21] depicted in Figs. 5 and 6 rather than from single fraction cell survival studies. In Fig. 5 it was demonstrated that at least one of the late effects (lung) appears to exhibit LQ-L behavior with $D_T \approx 2\alpha/\beta$ Gy and γ the tangent at D_T. In Fig. 6 one of the three spinal cord syndromes (cervical vascular damage) appears to exhibit LQ-L behavior with γ the tangent at D_T. It is reasonable to expect that other examples of LQ-L behavior for late reactions will be found. In Fig. 7, under the assumption that the late reaction exhibits LQ-L behavior, the model predicts that when cells with very different α/β are homogeneously irradiated with the goal of maintaining constant biological effect to the higher α/β reaction (e.g., tumor control) that the BED for the lower α/β reaction (e.g., late sequelae) initially increases as the number of fractions decreases, but eventually decreases again when very few fractions are used.

This reason for this can be explained, at least in principle, from the curves plotted in Fig. 8 which are loosely based on Fig. 22.6 in the chapter "Time, Dose and Fractionation" in Hall's radiobiology textbook.[2] Hall points out that for tumor and other early effects that the α/β ratio is generally large (blue line), that α dominates at low doses, and that the dose-response curve on the LLP has a marked initial slope and does not bend until higher doses. For late effects the α/β ratio is assumed to be small (black line) so the dose-response curve appears "more curvy." In this example the low α/β response is depicted as being relatively less severe per unit of dose at low dose. The high and low α/β LQ curves eventually intersect at some moderate dose beyond which the low
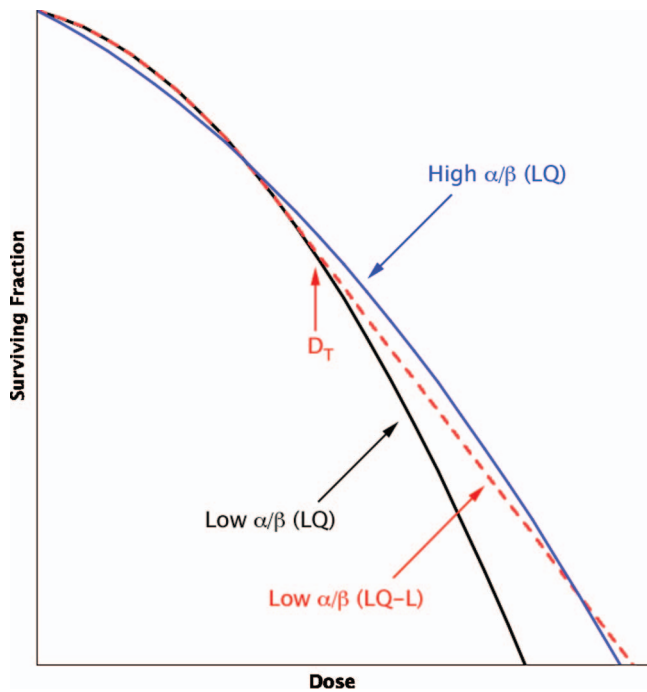
FIG. 8. Demonstration of principle illustrating how α/β differences might be exploited if the low α/β response exhibits LQ-L behavior and D_T $\approx 2\alpha/\beta$ Gy. The LQ dose-response reactions for low α/β (black line, e.g., late effects) are initially less severe but more curved than the high α/β (blue line, e.g., tumor) reactions. This therapeutically favors a large umber of small fractions. If the low α/β reactions instead exhibit LQ-L behavior (red dashed line) and the response curve becomes linear at some intermediate dose while the curve for high α/β reactions continues to bend, there could be some therapeutic advantage to using a few fractions of high dose. If, on the other hand, the tumor exhibits LQ-L behavior while the late effects remain LQ, then dose fractions greater than the tumor D_T could be therapeutically disadvantageous even if both the tumor and late effects are low α/β.

α/β LQ reactions become progressively more severe with dose compared to the high α/β LQ reactions because the low α/β LQ curve is bending downward more rapidly with increasing dose than is the high α/β curve. If the low α/β curve represents late effects, then the late effects will be more severe when large fractions are used, even if the high α/β reactions (e.g., tumor) are adjusted for constant effect. This therapeutically favors fractionation regimens that employ a large number of small fractions and is one of the basic rationales for conventionally fractionated therapy regimens.

If, on the other hand, the low α/β reactions were to exhibit LQ-L behavior (red dashed line) and become linear on the LLP at some intermediate dose, then the low α/β LQ-L curve will straighten in this intermediate dose range rather than continuing to bend, while the curve for the high α/β reaction can be expected to continue bending until a much higher dose. In this case the high α/β curve and the low α/β LQ-L curve intersect at some moderate dose, and then intersect again at some very high dose, beyond which the low α/β LQ-L reactions once more become relatively less severe than the high α/β reactions. It is unknown at this time if this theory has any clinical applicability, and this upper dose range of relatively less severe reactions for low α/β, if it

exists, could well occur at such a high dose that functional organ tolerance is exceeded even though there may be some surviving cells.

One implication of Figs. 7 and 8, however, is that it might be possible to exploit α/β differences by using a few fractions of very high dose when treating a tumor with a high α/β that is intermixed with tissues or organs of low α/β if, and only if, the reactions of those low α/β tissues or organs exhibit LQ-L behavior. One advantage of using a few large fractions compared to conventional fractionation, assuming late sequelae being equal, might be the avoidance of tumor repopulation. This possibility should be explored in the laboratory. A hypothetical experiment could be a tumor with a high α/β in the lungs of mice. This idea is based on the observation in Fig. 5 that a late lung reaction of mice appears to exhibit LQ-L behavior.

On the other hand, for a tumor such as prostate cancer whose low α/β of about 3 Gy is similar to the α/β of the surrounding organs and tissues, speculation exists that there may be little advantage in terms of late sequelae to any particular fractionation so long as the fraction dose is adjusted to maintain the desired probability of tumor control.[22] This may not be the situation, however, if the tumor's dose-response is LQ-L, a possibility suggested by Fig. 4, while one or more of the related late effects remain LQ as in Fig. 5. In that case, even though both have low α/β, the LQ late effects will become relatively more severe compared to the LQ-L reactions of the tumor at doses greater than D_T (for the tumor) as also illustrated in Fig. 8. The same basic rational also applies to tumors with high α/β that exhibit LQ-L behavior when late effects are simply LQ. This will be of greatest concern when both the tumor and surrounding tissues are irradiated to the same dose. The steep dose gradients that are now achievable using intensity modulated planning and delivery technologies work to reduce the severity of late effects by reducing the dose to the tissues surrounding the tumor. Still, it may be prudent to consider D_T for the tumor reactions as the upper limit of fraction doses that should be considered.

When the clinical dose-response reactions of tumor and/or other tissues or organs exhibit LQ-L behavior, intercomparison of conventional and hypofractionation regimens using LQ-L models should provide more accurate results than the LQ model because LQ-L better fits a wider range of dose for whatever experimental data is available. The LQ-L formulation proposed here and that of Park et al.[12] are attractive for the clinic because the transition dose D_T clearly identifies the upper limit to which the LQ formulation should be applied. Only for fractions of size greater than D_T need the transition to final linearity be applied.

V. CONCLUSIONS

Limitations of the LQ formulation are that it is not compatible with some examples of clonogenic cell survival and that it improperly models the experimentally observed exponential decrease of cell survival with dose at high dose. Fitting a linear-quadratic-linear curve to the experimental dose-

response data is a simple remedy to this problem. LQ-L models will probably find their greatest clinical utility when intercomparing conventional and hypofractionated regimens for those reactions which exhibit LQ-L dose-response and are of low α/β because the transition to final linearity could well fall somewhere within the range of doses that might be considered for hypofractionation. The LQ-L formulation proposed here can fit a wide variety of dose-response data over a very wide range of dose yielding a dose-range-independent approximation for α/β, which, in turn, enables BED to be intercompared over a wide range of dose. The LQ-L transition dose D_T and γ, the $\log_e$ cell kill per Gy in the final linear portion of the survival curve, can be determined by fitting the LQ-L model to experimental dose-response and/or multiple fraction isoeffect studies. The simplification of γ being the tangent at D_T appears to have wide, but not universal, applicability. The term D_T carries intuitive clinical significance because it describes the dose at which the linear-quadratic model ends and the final linear tail of the dose-response curve, on the log-linear plot, begins. When late reactions are known to be LQ, it may be prudent to consider D_T for the tumor reactions as the upper limit of fraction doses that should be considered.

[a)] Electronic mail: astrahan@usc.edu; Telephone: 323-865-3091; Fax: 323-865-0000

[1] H. Withers, "Biologic basis for altered fractionation schemes," Cancer **55**, 2086–2095 (1985).

[2] E. Hall, "Cell survival curves," in *Radiobiology for the Radiologist*, 5th ed. (Lippincott Williams & Wilkins, Philadelphia, 2000), pp. 35–37.

[3] M. Elkind and H. Sutton, "X-ray damage and recovery in mammalian cells in culture," Nature (London) **184**, 1293–1295 (1959).

[4] G. Barendsen, "Dose fractionation, dose rate and isoeffect relationships for normal tissue responses," Int. J. Radiat. Oncol., Biol., Phys. **8**, 1981–1997 (1982).

[5] J. Fowler, "The linear-quadratic formula and progress in fractionated radiotherapy," Br. J. Radiol. **62**, 679–694 (1989).

[6] B. Jones, L. Tan, and R. Dale, "Derivation of the optimum dose per fraction from the linear quadratic model," Br. J. Radiol. **68**, 894–902 (1995).

[7] H. Thames *et al.*, "Time-dose factors in radiotherapy, A review of the human data," Radiother. Oncol. **19**, 219–235 (1990).

[8] J. Fowler, W. Tome, J. Fenwick, and M. Mehta, "A challenge to traditional radiation oncology," Int. J. Radiat. Oncol., Biol., Phys. **60**, 1241–1256 (2004).

[9] L. Garcia, D. Wilkins, G. Raaphorst, "α/β ratio, a dose range dependence study," Int. J. Radiat. Oncol., Biol., Phys. **67**, 587–593 (2007).

[10] M. Guerrero and X. Li, "Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy," Phys. Med. Biol. **49**, 4825–4835 (2004).

[11] J. Z. Wang, N. A. Mayr, and W. T. C. Yu, "A generalized linear-quadratic formula for high-dose-rate brachytherapy and radiosurgery," Int. J. Radiat. Oncol., Biol., Phys. **69**, S619–S620 (2007).

[12] C. Park, L. Papiez, S. Zhang, M. Story, and R. Timmerman, "The unifying (hybrid) survival curve and single fraction equivalent dose: Useful tools in understanding the potency of ablative radiation therapy," Int. J. Radiat. Oncol., Biol., Phys. **70**, 847–852 (2008).

[13] K. Atwood and A. Norman, "On the interpretation of multi-hit survival curves," Proc. Natl. Acad. Sci. U.S.A. **35**, 696–709 (1949).

[14] M. Carlone, D. Wilkins, and G. Raaphorst, "The modified linear quadratic model of Guerrero and Li can be derived from mechanistic basis and exhibits linear-quadratic-linear behavior," Phys. Med. Biol. **50**, L9–L15 (2005).

[15] T. Puck and P. Markus, "Action of x-rays on mammalian cells," J. Exp. Med. **103**, 653–666 (1956).

[16] H. Thames and H. Withers, "Test of equal effect per fraction and estimation of initial clonogen number in micro colony assays of survival after fractionated irradiation," Br. J. Radiol. **53**, 1071–1077 (1980).

[17] A. Han, A. C. Hill, and M. Elkind, "Repair of cell killing and neoplastic transformation at reduced dose rates for ^{60}Co γ-rays," Cancer Res. **40**, 3328–3332 (1980).

[18] K. Stone, H. Wunderli, G. Mickey, and D. Paulson, "Isolation of a human prostate carcinoma cell line (DU-145)," Int. J. Cancer **21**, 274–281 (1978).

[19] J. Leith *et al.*, "Radiobiological studies of PC-3 and DU-145 human prostate cancer cells, x-ray sensitivity in vitro and hypoxic fractions of xenografted tumors in vivo," Int. J. Radiat. Oncol., Biol., Phys. **25**, 283–287 (1993).

[20] B. G. Douglas and J. F. Fowler, "The effect of multiple small doses of X-rays on skin reactions in the mouse and a basic interpretation," Radiat. Res. **66**, 401–426 (1976).

[21] A. J. van der Kogel, "Spinal cord tolerance: Time-dose-isoeffect relationships," in *Late Effects of Radiation on the Spinal Cord*, (Radiobiological Institute of the Organization for Health Research TNO, Rijswijk, The Netherlands, 1979), pp. 101–121.

[22] D. Brenner, "Hypofractionation for prostate cancer radiotherapy—what are the issues?," Int. J. Radiat. Oncol., Biol., Phys. **57**, 912–914 (2003).