



## Modelling of fractionation

## Use of the LQ model with large fraction sizes results in underestimation of isoeffect doses



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## ABSTRACT

**Purpose:** To test the appropriateness of the linear-quadratic (LQ) model to describe survival of jejunal crypt clonogens after split doses with variable (small 1–6 Gy, large 8–13 Gy) first dose, as a model of its appropriateness for both small and large fraction sizes.

**Methods:** C3Hf/KamLaw mice were exposed to whole body irradiation using 300 kVp X-rays at a dose rate of 1.84 Gy/min, and the number of viable jejunal crypts was determined using the microcolony assay. 14 Gy total dose was split into unequal first and second fractions separated by 4 h. Data were analyzed using the LQ model, the lethal potentially lethal (LPL) model, and a repair-saturation (RS) model.

**Results:** Cell kill was greater in the group receiving the larger fraction first, creating an asymmetry in the plot of survival vs size of first dose, as opposed to the prediction of the LQ model of a symmetric response. There was a significant difference in the estimated  $\beta$ s (higher  $\beta$  after larger first doses), but no significant difference in the  $\alpha$ s, when large doses were given first vs small doses first. This difference results in underestimation (based on present data by approximately 8%) of isoeffect doses using LQ model parameters based on small fraction sizes. While the LPL model also predicted a symmetric response inconsistent with the data, the RS model results were consistent with the observed asymmetry.

**Conclusion:** The LQ model underestimates doses for isoeffective crypt-cell survival with large fraction sizes (in the present setting, >9 Gy).

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While many innovations have improved the outcome of radiotherapy for lung and other cancer types (e.g. new prognostic parameters, better visualization, improved dosimetry), this progress has been only moderate, and lung tumors continue to have a grim prognosis if not detected early [1]. It is widely believed that distant metastasis is the main problem and this has led to implementation of adjuvant chemotherapy as standard of care. However, the impact on overall survival of a decrease in distant metastases of 5–10% is difficult to detect, given the high local recurrence rate. This situation has been changing in recent years on account of new approaches that have improved local control for certain tumor sites; an example of these new approaches is stereotactic body radiotherapy (SBRT), an image-guided hypofractionated radiotherapy that delivers a high dose of radiation in a single or a few large dose fractions [2]. Its efficacy has been demonstrated in a number of studies [3] including centrally located lung tumors [4], while others have questioned its use for stage I peripheral tumors [5].

Implementation of these hypofractionation schemes has required decisions about tolerance doses, and in most cases calculations have been based on clinical experience with methods based on the linear-quadratic (LQ) model. This clinical experience is largely derived from the response to modest departures from conventional fractionation, i.e. doses per fraction near 2 Gy – much smaller than those used in SBRT. However, classical cell-survival curves are increasingly linear at high doses, and if this were the correct description of the response of tumors and tissues to fractionated radiotherapy, the LQ-based methodology would be expected to underestimate isoeffective doses when the fraction size is large. While some have argued that the absence of clinical problems is reason enough for the LQ's continued use [6], for others a few observed deviations at high-doses have suggested that the LQ is not appropriate [7], and additional evidence indicates that the LQ model becomes less accurate at high doses [8]. This has led to the development of modified approaches based on corrections to the continuously curving LQ survival model [8–13]. Nevertheless, the LQ approach is the most widely used to estimate isoeffect doses for SBRT, and the question remains whether it is appropriate for clinical use. In particular, does it overestimate the effect of large dose fractions (i.e. underestimate isoeffective doses after large dose fractions)?

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Light is thrown on this question by reexamination of results from HR Withers's group from the late 1960s – early 1970s, where the responses of jejunum and testis to split doses were studied using the microcolony assay [14,15]. An unusual aspect of these experiments was that the total dose was held constant (e.g. 16 Gy for the jejunum), while the size of the first dose varied from small to large (e.g. 1 + 15 Gy, 2 + 14 Gy, 3 + 13 Gy, ..., 8 + 8 Gy, ..., 13 + 3 Gy, 14 + 2 Gy, 15 + 1 Gy, total dose = constant = 16 Gy). Since the interval between doses was long enough to expect complete repair, according to the LQ model a graph of the resulting number of surviving cells per crypt vs size of first dose should have had a symmetric egg-like shape with maximum survival observed when the total dose was equally divided into two 8-Gy fractions. Instead, it was observed that the curve was asymmetrically shifted toward higher survival after the smaller first doses, suggesting an unequal effect of a given dose, depending on whether it was delivered as the first or the second dose.

This suggestive (but inconclusive) evidence of possible failure of the LQ model led us to repeat the split-dose experiment with jejunum in greater detail. Here we report the results of these experiments, which confirm the asymmetry of response observed by Withers et al. [14,15]. The results are analyzed in terms of the LQ model, as well as two different models of DNA repair. Finally, we discuss the significance of our findings with regard to tolerance calculations for SBRT treatments.

## Material and methods

### Mice

Groups of 8 female C3Hf/KamLaw mice were exposed to whole body irradiation using 300 kVp X-rays at a dose rate of 1.84 Gy/min. The first fraction ( $x_1$ ) was given at 7 AM at which time jejuna were also collected from non-irradiated controls. The second fraction ( $x_2$ ) was given 4 h later when repair was assumed to be complete. The first dose varied from 0.5 to 13.5 Gy, and the total dose was fixed at 14 Gy. To validate significant differences observed in survival based on sequence of doses, the experiment was performed four times for  $\times 1 = 1.5$  and 2 Gy, three times for  $\times 1 = 3$  and 4 Gy, and once for the remaining pairings.

### Microcolony assay

The number of viable jejunal crypts was determined using the microcolony assay [16]. Mice were sacrificed at 3.5 days after the second fraction, and 2-cm segments of jejunum resected and fixed in 10% neutral buffered formalin. Tissue was embedded in paraffin, then four 4  $\mu$ m transverse slices were stained with hematoxylin and eosin as shown in Fig. 1. The number of regenerating crypts per transverse section (selected examples shown in Fig. 1 by arrows) was scored microscopically and averaged over the 4 sections per animal. All slides were scored by a single observer (KAM) blinded to treatment group.

### Data analysis

The results were analyzed in terms of the LQ model, and in terms of Curtis' lethal-potentially lethal (LPL) [17] and Kiefer's repair-saturation (RS) [18] models of post-radiation DNA repair. Let total dose = 14 Gy =  $x_1 + x_2$ , and  $\ln S = \ln$  (cell surviving fraction). Assuming a Poisson distribution of lethal events, the observed cell surviving fraction  $S$  is given by

$$S = -(1/150) \ln[1 - (\text{number of regenerating crypts/circumference})/160] \quad (1)$$

where 150 = estimated number of clonogens/crypt [19] and 160 = observed number of crypts per circumference in the controls. The procedures for the 3 models were as follows.

LQ model (complete repair): log surviving fraction was regressed against  $x_1^2 + x_2^2$  using the model:

$$\ln S = -14\alpha - \beta(x_1^2 + x_2^2) = \beta_0 + \beta_1(x_1^2 + x_2^2) \quad (2)$$

so that  $\alpha = -(\text{regression constant})/14 = -\beta_0/14$ , and  $\beta = -\text{regression slope} = -\beta_1$ . Next we checked for an effect of the sequencing of the doses by defining  $\gamma = 1$  if  $x_1 > x_2$ ,  $\gamma = 0$  if  $x_1 < x_2$ , and  $x_{12} = \gamma * (x_1^2 + x_2^2)$ . The regression model was modified to

$$\ln S = \beta_0 + \beta_1(x_1^2 + x_2^2) + \beta_2\gamma + \beta_3x_{12} \quad (3)$$

If  $\beta_2$  is significant,  $\alpha$  depends on the sequencing of doses; if  $\beta_3$  is significant,  $\beta$  depends on the sequencing of doses. For each of the fitting scenarios,  $\alpha/\beta$  was estimated using nonparametric bootstrapping (whence its estimate does not exactly correspond to the ratio of the estimates of  $\alpha$  and  $\beta$ ). Finally, isoeffect doses were

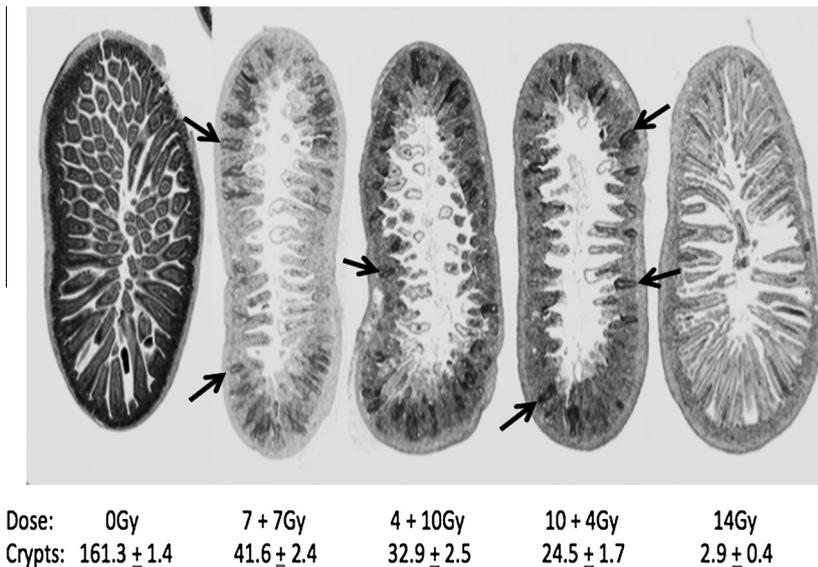


Fig. 1. Jejunal sections stained with H&E, 100 $\times$  magnification. Arrows point to examples of regenerating crypts.

calculated for two clinical scenarios, using the formulation whereby the biological effect of total dose  $D$  given in fractions of size  $x$  is given by  $D(\alpha/\beta + x)$ .

LPL and RS models: These are described by two ordinary differential equations that quantify the hypothetical evolution in time of repairable ( $u$ ) and non-repairable ( $v$ ) lesions:

$$\begin{aligned} \frac{du}{dt} &= \delta_1 r - \frac{\lambda_1}{1 + \epsilon u} - \lambda_2 u - \lambda_3 u^2 \\ \frac{dv}{dt} &= \delta_2 r + \lambda_2 u + \lambda_3 u^2 \end{aligned} \tag{4}$$

where  $r$  = dose rate,  $\delta_1 r$  and  $\delta_2 r$  = rates of induction of potentially lethal and lethal lesions, respectively, and  $\lambda_1$ ,  $\lambda_2$ , and  $\lambda_3$  correspond to the rates of repair, fixation, and binary misrepair, respectively.  $\epsilon$  is the parameter for repair saturation in the RS model: as the amount of repairable damage increases, the rate of increase in its repair rate slows. Setting  $\delta_2$ ,  $\lambda_2$ , and  $\epsilon$  to 0 reduces the equations to those of the LPL formalism [17]. The RS model [18] results from restricting  $\delta_2$  and  $\lambda_3$  to 0.

The differential equations for each model were solved numerically [20] using the Python wrapper available in the scipy package [21] with initial conditions of  $u(t)$ ,  $v(t) = 0$  and dose rate  $r = 110.4$  Gy/h. The solution was then fit nonlinearly against the observed data, comparing the prediction of the model (surviving fraction =  $S = \exp[-u(T)]$ ), where  $T$  = a time that is long compared with 4 h) with the observed cell surviving fraction (Eq. (1)).

**Results**

*Microcolony data*

Between treatment groups receiving the same-sized doses but in reverse sequence, the cell kill was greater in the group receiving the larger fraction first with one statistically non-significant exception. The results of the comparisons are summarized in Table 1 in terms of number of surviving crypt clonogens per 1000 at risk. The difference in log survival was statistically significant ( $p < 0.05$ ) for the 1.5/12.5, 2/12, 3/11, and 4/10 Gy treatment pairs.

*LQ model*

The fit of the basic LQ model (Eq. (2)) to the data set out in Table 1 is shown by the dashed curve in Fig. 2, where the asymmetry in the data is evident. This asymmetry was modeled as described by Eq. (3). The coefficient  $\beta_2$  (Eq. (3)) was not significant ( $p = 0.279$ ), indicating that  $\alpha$  did not depend significantly on the sequencing of the doses, whereas  $\beta_3$  was significant ( $p = 0.015$ ), indicating that the LQ parameter  $\beta$  changes with sequencing of the doses. The estimates of  $\alpha$  and  $\beta$  (with 95% CI) are shown in Ta-

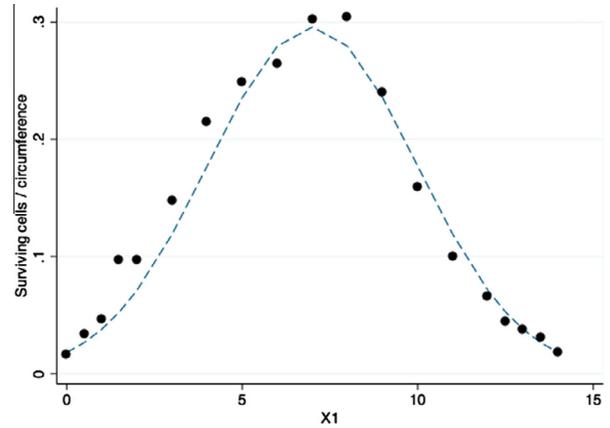


Fig. 2. Egg-shaped survival curve of jejunal crypt survival after exposure to two unequal fractions, showing fit of LQ model (Eq. (2)).

ble 2 for 3 conditions:  $0 < x_1 < 14$  (all data), data where  $x_1 > x_2$ , and data where  $x_1 < x_2$ .

Interestingly, the ratio  $\alpha/\beta$  is about 20% smaller when the large dose is given first (7.8 Gy vs 9.5 Gy). This has implications for tolerance calculations using the LQ model, as follows. Suppose we want to estimate the total dose given in 12-Gy fractions that is equivalent for jejunal tolerance to 60 Gy given in 2-Gy fractions. If we carry out the LQ-model calculation using the estimate  $\alpha/\beta = 9.46$  Gy based on “small” doses given first in the split-dose experiments described above, we have  $D(2\text{-Gy fractions}) * (\alpha/\beta + 2) = 60 * 11.46 = D(12\text{-Gy fractions}) * (\alpha/\beta + 12) = D(12\text{-Gy fractions}) * 21.46$  so that  $D(12\text{-Gy fractions}) = 32$  Gy. If we carry out the same calculation, but substitute  $\alpha/\beta = 7.80$  Gy for the large-fraction tolerance estimate and retain  $\alpha/\beta = 9.46$  Gy for the small-fraction tolerance estimate, we have  $D(2\text{-Gy fractions}) * (\alpha/\beta + 2) = 60 * 11.46 = D(12\text{-Gy fractions}) * (7.8 + 12) = D(12\text{-Gy fractions}) * 19.8$  so that  $D(12\text{-Gy fractions}) = 34.7$  Gy. While the absolute size of the difference depends on the details of the experimental design and methods described here, the difference is significant since the  $\beta$ s were significantly different.

*LPL and RS models*

The fit of the LPL model was essentially the same as that of the LQ model (Eq. (2)), i.e. the asymmetry shown in Fig. 2 (and summarized in Tables 1 and 2) was not reproduced (results not shown). An asymmetrical response curve was however observed using the RS model, i.e. with the inclusion of repair saturation (i.e.  $\epsilon > 0$ ), as shown in Fig. 3. The essential differences between the models are the parameter  $\epsilon$  (RS model) and the quadratic fixation term (binary misrepair in the LPL model). Binary misrepair was neither necessary nor sufficient for asymmetry.

**Discussion**

Here we report the results of split-dose experiments using an in vivo endpoint (jejunal crypt clonogen survival), with unequal first doses (first doses small 1–6 Gy vs large 8–13 Gy) separated by 4-h intervals, but fixed total dose, aimed at the question of the suitability of the LQ model for tolerance calculations for SBRT. For these doses the LQ model (with complete repair) would predict a survival response that was “egg” shaped and symmetric about 7 Gy. The results however show an asymmetric survival response (Fig. 2), a conclusion that is based on significantly lower survival when the larger dose was given first vs smaller dose given first (Table 1). Analysis of the data using the LQ model (Table 2)

Table 1  
Observed 1000 \* surviving fraction, small dose + large dose vs large dose + small dose.

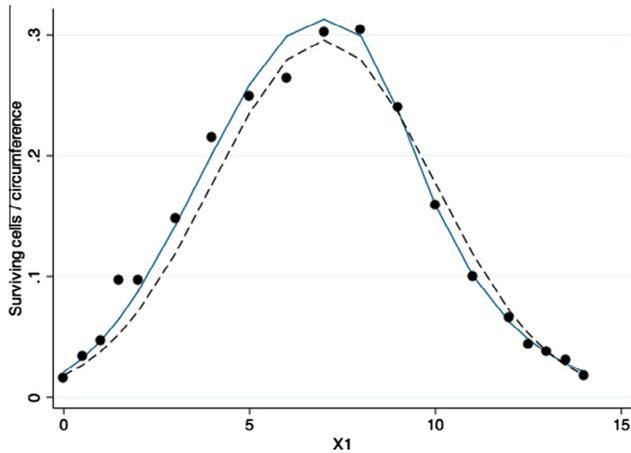
Groups compared:	1000 * surviving fraction small + large	1000 * surviving fraction large + small	p*
0 + 14 vs 14 + 0	0.121		–
.5 + 13.5 vs 13.5 + .5	.226	.208	0.889
1 + 13 vs 13 + 1	.311	.256	0.682
1.5 + 12.5 vs 12.5 + 1.5	.653	.296	<0.00005
2 + 12 vs 12 + 2	.649	.444	.0004
3 + 11 vs 11 + 3	.991	.671	0.011
4 + 10 vs 10 + 4	1.446	1.066	0.011
5 + 9 vs 9 + 5	1.670	1.614	0.261
6 + 8 vs 8 + 6	1.775	2.042	0.249
7 + 7	2.027		–

\* Unpaired, unequal variance t-test of null hypothesis: mean ln(surviving fraction) is independent of sequence of dose fractions.

**Table 2**  
Estimates of LQ-model parameters for different subsets of the data (95% CI given in parentheses).

Data	$\alpha$ ( $\text{Gy}^{-1}$ )	$\beta$ ( $\text{Gy}^{-2}$ )	$\alpha/\beta$ ( $\text{Gy}$ ) <sup>*</sup>
All data	0.245 (0.227–0.264)	0.0284 (0.0266–0.0303)	8.64 (7.36–9.91)
Large dose + small dose	0.237 (0.211–0.264)	0.0304 (0.0278–0.0330)	7.80 (5.92–9.68)
Small dose + large dose	0.257 (0.234–0.280)	0.0261 (0.0238–0.0284)	9.46 (7.22–11.70)

\* Estimate of  $\alpha/\beta$  from nonparametric bootstrapping differs slightly from ratio of estimates of  $\alpha$  and  $\beta$ .



**Fig. 3.** Fits of the RS (solid) and LQ (dash) models.

demonstrates the dependence of the estimated LQ parameter  $\beta$  on size of the first dose (significantly larger when the larger dose is given first), as does the ratio  $\alpha/\beta$  (smaller for larger first doses). The consequence of this is that, in terms of the results of the experiments described here, the LQ model based on conventional dose fractionation (small fraction sizes) underestimates tolerance doses for large fraction sizes. These findings are consistent with the possibility that the target-cell survival curve is increasingly linear with increasing dose. Thus they are consistent with the various approaches that model increasing linearity of the survival curve at higher doses per fraction [8–13].

The clinical relevance of the effect found by this study (approximately 8% underestimation of isoeffect dose) lies in the observed significant difference between the  $\beta$ s after large vs small first dose, as the same would be expected to apply in various clinical situations. Although not specifically reflective of clinical practice, the experimental design (split unequal doses) and the endpoint (crypt-cell survival) used in this study were chosen for several reasons. First, this choice of doses permits a very parsimonious model of survival (Eqs. (2–3)) that is useful in accurate estimation of the parameters of the LQ model. Second, the microcolony assay is an *in vivo* endpoint that nevertheless allows exact determination of cell survival (as opposed to more qualitative endpoints such as proportion of animals displaying injury). This permitted application of more mechanistic models (Eq. (4)), to investigate possible reasons for the anomalous asymmetry in the results (Fig. 2). We conclude that, while the size of the effect (underestimation of isoeffect doses by the LQ model) will vary by clinical circumstance, the direction of the effect will be the same.

To investigate possible reasons for the unexpected asymmetry seen in Fig. 2, we also analyzed the data in terms of two mechanistic models of the relationship between dose and cell survival. Our fit of the lethal potentially lethal (LPL) model [17] resulted in a symmetric “egg”, consistent with the LQ result but inconsistent with the data. Only the inclusion of the saturation term ( $\varepsilon > 0$  in Eq. (4)) in the “repair saturation” (RS) model [18] gave results consistent (Fig. 3) with the observed asymmetry in survival response

to unequal doses with fixed total dose. It should be noted that the LPL and RS models depend on 3 independent variables (size of first dose, interval between fractions, and dose rate). Only 1 of these was varied in these experiments (size of first dose), so that a high degree of correlation holds between the parameters estimated from the present data. Future experiments will involve variation in each of the independent variables.

Our finding, that the Kiefer RS model gave a different fit to the data (Fig. 3) from that of the LQ model, seems to contrast with the finding of Brenner et al. [22], that predictions of the RS model conformed closely with those of the LQ model. This could be explained as follows. First, Brenner and colleagues did not model the split dose experiments that were the basis of this paper. Also, their method of solving the differential equations of the Kiefer model (nonsingular perturbation theory) was different from ours (numerical solution). Finally, they used the parameter  $\varepsilon$  as basis of the power series to expand the solution, which in our fit to the jejunum data we estimated at 0.04, some 2.5 times greater than the value used by Brenner et al. This would magnify the effect of dropping terms of order  $\varepsilon^2$  or smaller in the expansion of the solution.

It would clearly be of great interest to repeat these experiments using the endpoint local tumor control, to test whether our findings could be replicated in tumors. Some information can be gleaned from the surviving fractions set out in Table 1, extrapolated to the considerably higher split doses that would be required for local control in most of the experimental lines. Consider the well studied model FaDu, for which the split-dose TCD50 is 23.5 + 23.5 Gy [23]. Based on the results presented here, the big difference between survival after 1.5 + 12.5 vs 12.5 vs 1.5 suggests two TCD50 experiments, comparing TCD50s after split doses for pairings with similar ratios 1.5/14 = 0.107 and 12.5/14 = 0.893. For FaDu, the first TCD50 experiment might measure tumor recurrence after the split doses (with 4-h interval) 3.7 + 31.3, 3.9 + 32.2, 4.2 + 34.8, 4.4 + 36.6, and 4.6 + 38.4 Gy, whereas the second TCD50 experiment would measure the same for the reverse pairings 31.3 + 3.7, 32.2 + 3.9, 34.8 + 4.2, 36.6 + 4.4, and 38.4 + 4.6 Gy. The present results would be confirmed for this tumor model if TCD50 for the 2nd experiment was significantly lower than for the first experiment.

In summary, our results are consistent with hypothesis that use of the LQ model to estimate tolerance doses for SBRT treatments with large fraction sizes is likely to lead to underestimation of those doses. This finding is consistent with the possibility that the target-cell survival curve is increasingly linear with increasing dose.

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