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Original article

High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients

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ABSTRACT

Background and purpose: Two aspects of stereotactic radiotherapy (SRT) require clarification: First, are tumoricidal mechanisms at high-doses/fraction the same as at lower doses? Second, is single high-dose SRT treatment advantageous for tumor control (TCP) vs. multi-fraction SRT?
Material and methods: We analyzed published TCP data for lung tumors or brain metastases from 2965 SRT patients, covering a wide range of doses and fraction numbers. We used: (a) a linear-quadratic model (including heterogeneity), which assumes the same mechanisms at all doses, and (b) alternative models with terms describing distinct tumoricidal mechanisms at high doses.
Results: Both for lung and brain data, the LQ model provided a significantly better fit over the entire range of treatment doses than did any of the models requiring extra terms at high doses. Analyzing the data as a function of fractionation (1 fraction *vs.* >1 fraction), there was no significant effect on TCP in the lung data, whereas for brain data multi-fraction SRT was associated with higher TCP than single-fraction treatment.
Conclusion: Our analysis suggests that distinct tumoricidal mechanisms do not determine tumor control at high doses/fraction. In addition, there is evidence suggesting that multi-fraction SRT is superior to single-dose SRT.

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), are becoming increasingly accepted [1]. The spatial accuracy of dose delivery using these techniques (hereafter referred to as stereotactic radiotherapy, SRT) allows substantial dose escalation to the tumor [1].

Over the past three decades, radiotherapy design has been guided by the linear-quadratic (LQ) model [2–4]. Clinical results, even for some non-standard scenarios (hyperfractionation [5], high- *vs.* low dose-rate brachytherapy [6], prostate hypofractionation [7]) were consistent with LQ predictions. In contrast to earlier approaches [8–10], there have been no major failures.

Some investigators have argued that tumor eradication by large doses/fraction is dominated by distinct biological phenomena (e.g., damage to the tumor vasculature) that are qualitatively different from those operating at lower doses, and therefore are not accounted for by the LQ model [11–17]. By contrast, others argue [18,19] that SRT effectiveness is sufficiently explained by increased tumor doses, which destroy tumors largely through the same mechanisms that operate at lower doses.

In this paper, therefore, we address the question as to whether tumoricidal mechanisms at high-doses/fraction are the same as at lower doses – or are there new mechanisms at play specifically at high doses? We approach this question by analyzing a large data set for TCP *vs.* dose from SRT patients for lung tumors or brain metastases, covering a wide range of doses and fraction numbers. We analyze these data with the LQ model, which assumes the same mechanisms at all doses, and also with alternative models which incorporate extra terms describing different cell killing mechanisms at high doses.

Materials and methods

Data sets

Using the PubMed and Google Scholar databases, we searched for articles published in the past 15 years (up to 3/15/2013) that met the following criteria: (1) the reported radiotherapy regimens had to be classified as some form of SRT; (2) TCP had to be reported for $\geqslant$1 year following SRT for brain and/or lung tumors/metastases; (3) the number of fractions, and the dose per fraction had

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to be specified, preferably for more than one radiotherapy regimen; (4) information had to be provided allowing estimation of doses both to the isocenter and to the periphery (generally at least 80% of the prescribed isocenter dose covered the PTV).

We found 33 publications, which together contained data from 2965 patients, mostly treated for early-stage non-small cell lung cancer (NSCLC) or brain metastases. We extracted data on TCP values from 59 treatment regimens (Table 1). For each regimen, we extracted (or estimated, if it was not reported explicitly) the number of treated patients. The majority of treatment regimens (46 out of 59) were performed using LINAC equipment. There were no 3D-CRT regimens and only one IMRT regimen [20]. Median ages of the treated patients ranged from 52 to 79, with a mean of 67. Maximum tumor diameters ranged from 2.0 to 10.0 cm, with a mean of 5.2 cm.

Thirty-one percent of the patients were treated with single-fraction regimens with a median dose of 19.0 (range: 12.5, 25.0) Gy to the periphery and 25.0 (range: 16.9, 50.0) Gy to the isocenter. The median number of fractions for the fractionated regimes was 4 (range: 3, 15), and the median dose per fraction was 11.4 Gy (range: 3.2, 22.7) to the tumor periphery and 14.5 Gy (range: 4.0, 26.3) to the isocenter. The median TCP was 0.83 (range: 0.16 to 1.0). These values are consistent with previous studies of SRT (e.g., [21,22]). Increasing the minimum acceptable time for reported TCP after SRT from 1 years to 3 years did not change the TCP numbers dramatically (reducing the median TCP to 0.76), but dramatically reduced the number of available publications (from 33 to 15).

Table 1
Summary of the analyzed data sets. The majority of patients in the brain data set were treated for metastatic brain tumors, and the majority of patients in the lung data set were treated for early stage non-small cell lung cancer.

Published data set	Reference	Cancer site	Mean # of fractions	Mean isocentral dose/fraction (Gy)	# of patients
Chang	[44]	Brain	1.0	23.5	10
Chang	[44]	Brain	1.0	20.0	61
Chang	[45]	Brain	1.0	21.0	130
Chao	[46]	Brain	1.0	20.6	50
Chao	[46]	Brain	1.0	28.8	61
Engenhart	[47]	Brain	1.0	21.5	57
Lutterbach	[48]	Brain	1.0	22.5	101
Matsuo	[49]	Brain	1.0	25.0	30
Matsuo	[49]	Brain	1.0	50.0	30
Molenaar	[50]	Brain	1.0	16.9	29
Molenaar	[50]	Brain	1.0	23.8	29
Molenaar	[50]	Brain	1.0	28.8	28
Shiau	[51]	Brain	1.0	25.0	4
Shiau	[51]	Brain	1.0	33.0	30
Shiau	[51]	Brain	1.0	41.0	66
Shirato	[52]	Brain	1.0	25.0	39
Vogelbaum	[53]	Brain	1.0	30.0	9
Vogelbaum	[53]	Brain	1.0	36.0	12
Vogelbaum	[53]	Brain	1.0	48.0	27
Higuchi	[54]	Brain	3.0	20.0	43
Saitoh	[55]	Brain	3.0	13.0	15
Saitoh	[55]	Brain	3.0	14.0	34
Narayana	[20]	Brain	5.0	6.0	20
Ernst	[56]	Brain	5.0	7.8	22
Fritz	[57]	Lung	1.0	30.0	40
Hof	[58]	Lung	1.0	22.0	10
Hof	[58]	Lung	1.0	28.0	32
Trakul	[59]	Lung	1.0	30.0	48
Crabtree	[60]	Lung	3.0	21.8	76
Fakiris	[61]	Lung	3.0	26.3	70
Grills	[62]	Lung	3.0	22.5	209
Grills	[62]	Lung	3.0	25.0	22
Kopek	[63]	Lung	3.0	15.0	89
Koto	[64]	Lung	3.0	15.0	20
Olsen	[65]	Lung	3.0	21.4	111
Ricardi	[66]	Lung	3.0	18.8	62
Taremi	[67]	Lung	3.0	23.5	29
Taremi	[67]	Lung	3.0	22.5	19
Timmerman	[68]	Lung	3.0	22.5	55
Ng	[69]	Lung	3.2	18.9	20
Chang	[70]	Lung	4.0	15.2	130
Nagata	[71]	Lung	4.0	12.0	45
Shibamoto	[72]	Lung	4.0	11.0	4
Shibamoto	[72]	Lung	4.0	12.0	124
Shibamoto	[72]	Lung	4.0	13.0	52
Shirata	[73]	Lung	4.0	12.0	45
Taremi	[67]	Lung	4.0	15.1	41
Trakul	[59]	Lung	4.0	15.0	60
Grills	[62]	Lung	4.2	15.0	172
Haasbeek	[74]	Lung	4.9	15.5	193
Olsen	[65]	Lung	5.0	10.7	8
Olsen	[65]	Lung	5.0	11.9	11
Takeda	[75]	Lung	5.0	12.5	63
Grills	[62]	Lung	5.1	13.9	102
Koto	[64]	Lung	8.0	7.5	11
Shirata	[73]	Lung	8.0	7.5	29
Taremi	[67]	Lung	8.0	9.6	9
Taremi	[67]	Lung	10.0	5.8	10
Shirata	[73]	Lung	15.0	4.0	7

Radiobiological models

Our overall goal here is to investigate whether the SRT tumor control data imply that there are new tumoricidal mechanisms that determine tumor control at high SRT doses – mechanisms which are not present or have little effect at conventional radiotherapeutic doses. To accomplish this, we investigate whether the standard LQ model with heterogeneity can provide as good a description of the SRT data as can models with extra terms describing unique high-dose tumor control mechanisms.

The mechanistically-motivated model most often used to describe radiotherapeutic tumor control is the linear quadratic model [2–7], which has more recently been used to include heterogeneity, within and/or between tumors [23–28]. Consequently, as an example of a model which assumes that the same tumoricidal mechanisms operate at all radiation doses, we used the LQ model with heterogeneous tumor cell radiosensitivity (within a given tumor). Details of the LQ model, and its extension to heterogeneous tumor cell radiosensitivity, are given in Appendix A.

As examples of models which have been developed to describe the proposed and as yet not fully specified distinct tumoricidal mechanisms at high radiation doses, we used the Linear Quadratic Linear (LQL) [29,30], Universal Survival Curve (USC) [31], the Pade Linear Quadratic (PLQ) [32] formalisms (details are given in Appendix A).

It may be noted that models such as LQL, USC and PLQ assume homogeneous tumor sensitivity [29–32], though they are all amenable to extension including heterogeneous radiosensitivity. In the Results section we briefly describe results for heterogeneous versions of these models. However our primary focus here is to assess whether the extra high-dose terms in LQL, USC and PLQ are needed to describe the high dose SRT data, or whether the more established effects of heterogeneity are sufficient.

Model fitting and comparison procedures

For each radiotherapy regimen, there were n treated patients, and local tumor control was achieved for k of them, where $k = n$ TCP. Each radiobiological model predicted a TCP value (p), based on which the binomial log likelihood $\ln[L(p,n,k)]$ was calculated. Model fitting involved maximizing the sum of $\ln[L(p,n,k)]$ over all regimens.

Ranking of models by relative goodness of fit, taking into account sample size and parameter number, was based on the Akaike information criterion with sample size correction (AICc), which has gained widespread popularity for this purpose [33,34].

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For ranking non-linear models, AICc is preferable to methods that rely on reduced X^2 or R^2 [35–38]. Another useful property of AICc is that more than two models can be compared simultaneously, without the need for models to be "nested" or to belong to the same class. The model which has the lowest AICc value among those being compared is the best-fitting model, and those models which have AICc $\geqslant 6$ units higher than the best-fitting model have much poorer support from the data. More details about the use of AICc information criterion are in Appendix B. Confidence intervals for best-fit model parameter values were estimated by profile likelihood [39].

The relative importance of heterogeneous (HET) tumor cell radiosensitivity, compared with extra parameters which modify the cellular dose response shape at high doses, was calculated by the ratio $R = W_{HET}/W_{noHET}$, where W_{HET} is the sum of Akaike weights (described in Appendix B) for the heterogeneous LQL, PLQ, and USC models fitted to the same data, and W_{noHET} is the corresponding sum of Akaike weights for the homogeneous versions of the same models.

Results

Visual inspection of best-fit predictions from the analyzed models (Figs. 1 and 2) suggests that the LQ model with heterogeneous radiosensitivity provides a much better description of the SRT TCP data as compared with the models (LQL, PLQ and USC) which include an extra high-dose mechanism. Statistical analysis support for this difference in fit quality (by AICc, which accounts for model complexity as well as closeness of the fit to the data) is overwhelming both for the lung and for the brain data (Table 2): The LQL, PLQ and USC formalisms have AICc values which are hundreds of units higher than the heterogeneous LQ model, suggesting that these formalisms have effectively no support from the data, compared with the LQ model. In essence, given a biologically plausible initial number (N) of clonogenic tumor cells of 10^5, the LQL, PLQ and USC produced TCP dose responses which were too steep to describe the data well (Figs. 1 and 2). At larger values of N this effect became even stronger (not shown). Using this same initial number of clonogenic tumor cells (10^5), the LQ model with heterogeneity predicts a much shallower dose response, thereby bringing the model predictions much closer to the data. These results remained qualitatively unchanged regardless of whether we used doses to the isocenter (Figs. 1 and 2, Table 2), or to the periphery (not shown). They were also robust in response to altered assumptions about the α/β ratio: for example, when the ratio was increased from 10 Gy to 20 Gy, or was allowed to become freely adjustable.

The model comparison suggests that the addition of extra high-dose modification terms (implemented in LQL, USC, and PLQ models) had much less effect on model performance, than the inclusion of heterogeneous radiosensitivity, which dramatically improved agreement with SRT data for all models (Table 2, Figs. 1 and 2). The relative importance (R) of heterogeneous tumor cell radiosensitivity, compared with extra parameters which modify the cellular dose response shape at high doses, was quantified for the LQL, PLQ and USC as described in Materials and Methods. For the lung single-fraction data, $R \geqslant 98.7$, and R was effectively infinite ($>10^9$) for all other data subsets. In other words, accounting for variability in radiosensitivity is more important for describing the TCP data, than adjusting the details of cell survival curve shape at high doses.

To assess the effects of SRT fractionation on predicted TCP, single-fraction and multiple-fraction regimens were fitted separately. Using the best-fitting LQ model, for lung tumors fractionation effects could not be detected with confidence – when the model was fitted to single-fraction and multiple-fraction data

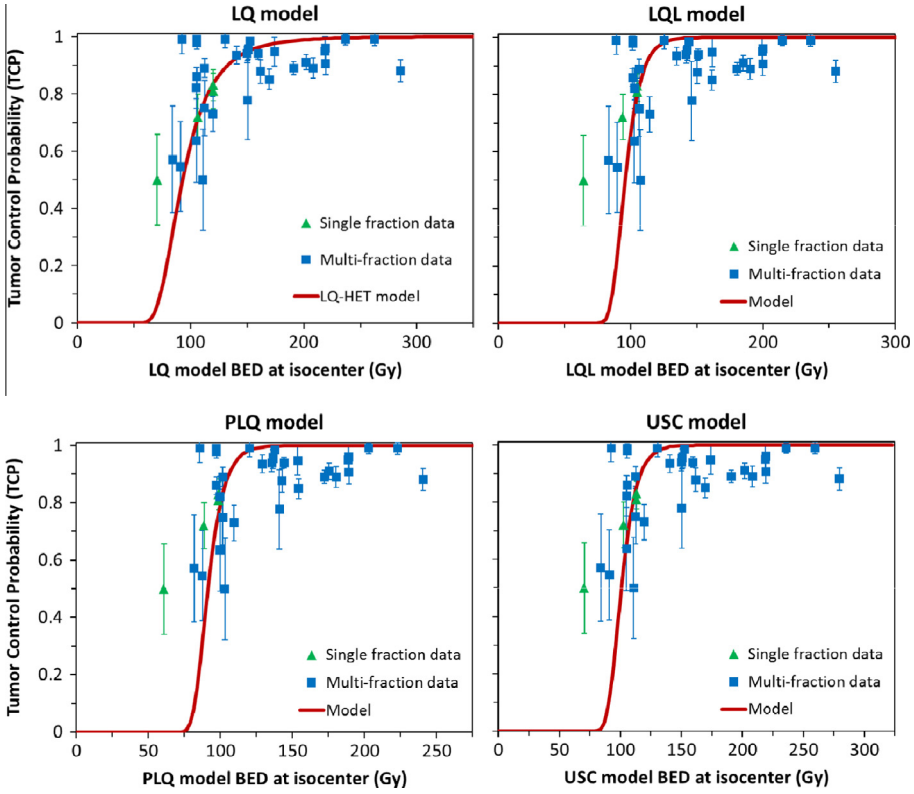

Fig. 1. Best fits to data on early-stage NSCLC from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity. In this and the following figures, error bars represent standard errors.

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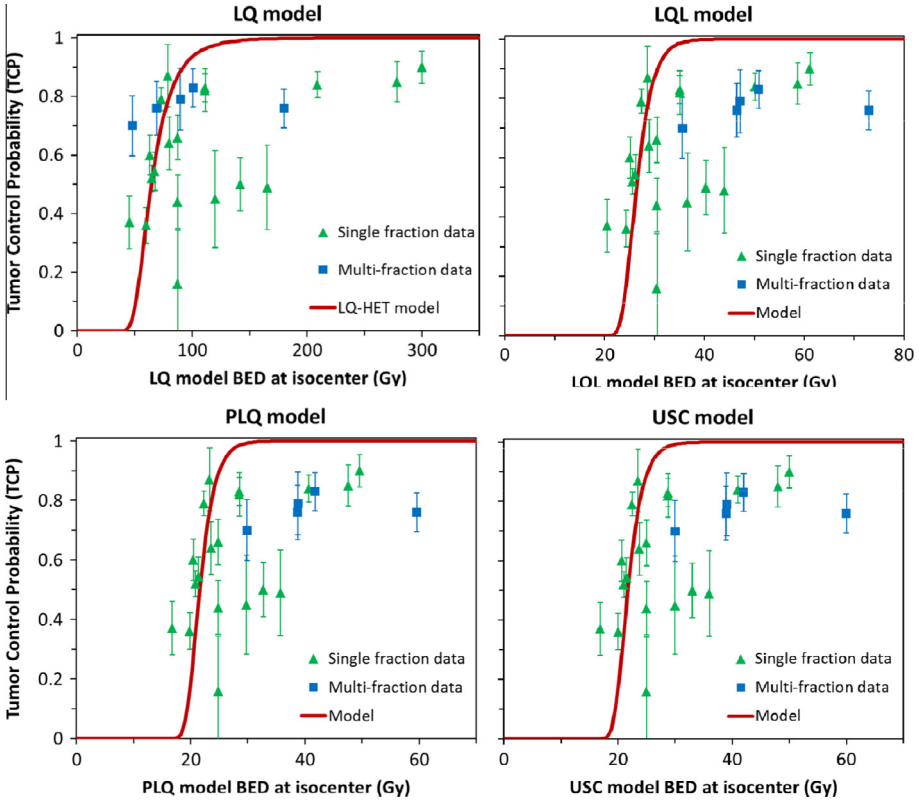

Fig. 2. Best fits to data on brain metastases from the LQ model with heterogeneous radiosensitivity (LQ), and from the LQL, PLQ and USC models with homogeneous radiosensitivity.

Table 2
Best-fit parameter values and relative fit quality assessment (by ΔAICc) for the LQ model with heterogeneous radiosensitivity (LQ), and for the LQL, PLQ and USC models with homogeneous radiosensitivity. Doses to the isocenter were used. The symbol p_1 refers to the extra parameter (compared with the LQ model) which is present in the LQL, PLQ and USC models (but has a different meaning and different units in each model, described in Appendix A). ΔAICc is the result of an information-theoretic analysis for comparing fit quality for different models on the same data. ΔAICc = 0 for the best-fitting model, and models with large ΔAICc values (>6) have much poorer support from the data. Details are discussed in the main text and in Appendix B.

Fraction #	Cancer site	Model	α (Gy^{-1}, 95% CI)			p_1 (95% CI)			ΔAICc
All	Lung	LQL	0.12	0.12	0.13	0.019	0.016	0.022	1664.4
All	Lung	PLQ	0.13	0.13	0.13	0.007	0.006	0.008	1661.6
All	Lung	USC	0.12	0.12	0.12	1.58	1.40	1.66	1607.7
All	Lung	LQ	0.40	0.39	0.42	–	–	–	0
1	Lung	LQL	0.47	0.45	0.48	∞	∞	∞	21.7
1	Lung	PLQ	47.81	46.43	49.27	14.11	13.69	14.52	0
1	Lung	USC	0.47	0.30	0.73	2.14	2.07	2.21	21.7
1	Lung	LQ	0.43	0.40	0.46	–	–	–	1.1
>1	Lung	LQL	0.26	0.25	0.26	∞	∞	∞	552
>1	Lung	PLQ	0.42	0.41	0.42	0.210	0.207	0.214	510.9
>1	Lung	USC	0.26	0.21	0.32	3.92	3.88	3.96	552
>1	Lung	LQ	0.40	0.39	0.41	–	–	–	0
All	Brain	LQL	0.45	0.45	0.45	0.873	0.841	0.913	991.4
All	Brain	PLQ	0.55	0.55	0.56	0.101	0.099	0.103	986.1
All	Brain	USC	0.55	0.45	0.64	1.83	1.82	1.84	987.1
All	Brain	LQ	0.58	0.57	0.59	–	–	–	0
1	Brain	LQL	0.56	0.55	0.56	∞	∞	∞	484.4
1	Brain	PLQ	15.85	15.69	16.01	4.16	4.12	4.20	67.7
1	Brain	USC	0.56	0.48	0.64	1.80	1.78	1.81	484.3
1	Brain	LQ	0.57	0.55	0.58	–	–	–	0
>1	Brain	LQL	0.35	0.34	0.37	∞	∞	∞	148.1
>1	Brain	PLQ	4.29	4.17	4.41	2.47	4.39	2.54	0
>1	Brain	USC	0.35	0.31	0.41	2.83	2.75	2.90	148.1
>1	Brain	LQ	0.66	0.62	0.72	–	–	–	65.9

separately, the 95% CIs for α overlapped (Table 2). However, for brain metastases the evidence from the data suggested that *multi*-fraction SRT regimens had higher effectiveness than single-fraction regimens (see α values and non-overlapping 95% CIs in Table 2, and curves in Fig. 3).

If the α/β ratio was increased from 10 Gy to 20 Gy and/or if peripheral doses were used, the evidence became too weak to differentiate between best-fit α values for single vs multiple-fraction SRT. For example, using isocenter doses and an α/β ratio of 20 Gy, the best-fit LQ α value for single-fraction SRT was 0.857 (95% CI:

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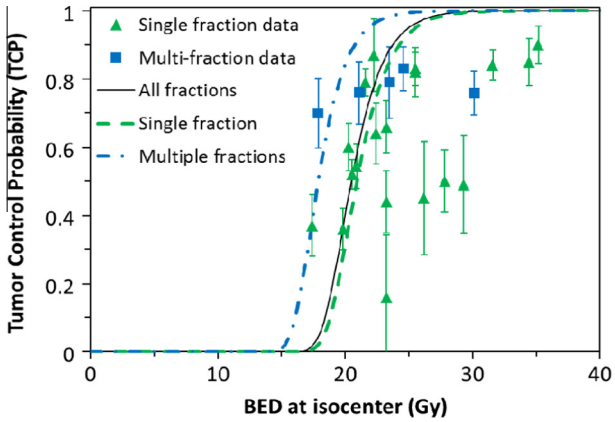

Fig. 3. Best fits of the LQ model with heterogeneous radiosensitivity to data on brain metastases treated with single-fraction vs. multiple-fraction SRT.

0.837, 0.877), and for multi-fraction SRT it was 0.834 (95% CI: 0.781, 0.898). Consequently, regardless of the α/β ratio, there was no support for the hypothesis that single-fraction regimens are inherently more effective than multiple fractions [14–17], and at a biologically plausible α/β ratio of 10 Gy there was some support for higher effectiveness of *multiple* fractions.

Discussion

The LQ model with heterogeneous radiosensitivity, which assumes that the same tumoricidal mechanisms operate at all doses and fraction numbers, provided a much better description of the SRT tumor control data over the entire dose range than did any of the models which assumed unique extra tumoricidal mechanism at high doses. These results, therefore, along with similarly motivated analyses [18,19,40], do not support the argument [11–17] that tumor response to high-dose SRT is fundamentally different from that which would be predicted from responses at conventional dose fractionations.

For example, proposed high-dose-specific tumoricidal mechanisms such as damage to the tumor vasculature [11–17] should enhance the TCP at high doses/fraction, predicting a steep dose response for TCP. The data, by contrast, support a shallow dose response which is reasonably explained by heterogeneity in radiosensitivity (and perhaps heterogeneity in other factors, such as spatial dose distribution [25–27]).

First, we conclude that because the formalisms which attempt to describe the tumor dose response at SRT doses by explicitly accounting for unique high-dose-specific tumoricidal mechanisms fit the data much worse than the heterogeneous LQ formalism which assumes the same mechanisms at all doses, there is no evidence from SRT tumor control data that the proposed high-dose-specific mechanisms dominate tumor control at high doses and/or at small fraction numbers. Rather, the effects of heterogeneous radiosensitivity dominate the comparatively subtle differences between the dose–response shapes produced by different radiobiological models [41]. In short, even if there are unique tumoricidal mechanisms at play at high doses, they are not the major determinants of tumor control by SRT.

Second, based on analyzing the data with the heterogeneous LQ model (including heterogeneity), there was no evidence that single-fraction SRT produces better tumor control than multi-fraction regimens. Instead, multi-fraction brain SRT was predicted to produce slightly better TCPs than single-fraction treatments for brain metastases. These conclusions are consistent with expected effects on hypoxic tumors, where fractionation allows tumor reoxygenation between fractions [41–43].

The strengths of our study include: (1) use of large amount of clinical data (from 2965 SRT-treated patients); (2) use of multiple radiobiological models, some of which (LQ) assume that the same tumoricidal mechanisms determine TCP at all doses and fraction numbers, whereas others (LQL, USC, PLQ) explicitly account for potential high-dose-specific tumoricidal mechanisms; and (3) use of a robust criterion (AICc) to compare support from the data for each of these models [33,34]. The main weaknesses (which are inherent in most similar analyses) involve: (1) fitting summary data vs. individual-patient data; and (2) oversimplification of tumor radiation response by not accounting for effects of tumor size and stage, time after SRT when TCP was reported, patient age and sex, calendar year and institution-specific factors, and many other potential effects. However, because these weaknesses are the same for all considered models, relative comparison of model fit quality can provide insights into how well (or how poorly) does each model capture the main features of tumor response to SRT.

In summary, the TCP data from modern SRT can be reasonably described by models which assume that the same tumoricidal mechanisms determine TCP at all doses and fraction numbers. Consequently, the use of such models remains a clinically successful and mechanistically plausible approach for guiding radiotherapy design.

Conflict of interest

None.

Appendix A

A.1. Radiobiological models

A.1.1. Linear quadratic (LQ) model

The LQ model is a mechanistic consequence of repair/misrepair kinetics of radiation-induced DNA double strand breaks (DSBs) [76,77]. Differences in fractionation response between tissues [78] are quantified through differences in the ratio of parameters α and β, and this ratio (here labeled as $r = \alpha/\beta$ for convenience) can be directly derived from clinical data.

The LQ formalism postulates that the fraction of cells which survive an acute radiation dose d is determined by the following expression [79,80].

$$S_{lq} = exp[-\alpha d - \alpha/r d^2] \quad \text{(A1)}$$

For simplicity, we assume that the heterogeneity in tumor cell radiosensitivity applies to the linear term (α) of the LQ model, because this term was shown to be most influential numerically [23,25,81]. Mathematically, this is implemented as follows.

We introduce a dummy variable a, which is randomly distributed, from zero to infinity, according to the Gamma distribution, with a mean value of α and a shape parameter g (restricted to integers $\geqslant 2$ for convenience). The Gamma distribution was selected instead of the Gaussian distribution because, consistently with biological plausibility, it converges to zero at $\alpha = 0$ (whereas the Gaussian distribution does not), and generates a simple analytic solution for TCP for several tested models (see below).

The probability density function (*PDF*) is:

$$PDF = a^g exp[-(g+1)a/\alpha](g+1)^{(g+1)}/(\alpha^{(g+1)}g!) \quad \text{(A2)}$$

The clonogenic survival probability (S_{het}) for the heterogeneous population of tumor cells exposed to a radiotherapy regimen composed of m acute dose fractions with d Gy per fraction (and assuming sufficient time for complete DNA damage repair between fractions) is calculated as follows:

$$S_{het} = \int_0^\infty PDF\, S_{lq} da = exp[(g+1)\ln(g+1)]r^{(g+1)}/(\alpha m d(d+1) + r(g+1))^{(g+1)} \quad (A3)$$

Alternatively, S_{het} can also be expressed as function of BED calculated using the LQ model:

$$S_{het} = (g+1)^{(g+1)}/(\alpha BED + g + 1)^{(g+1)} \quad (A4)$$

We assume that tumor control occurs when all tumor clonogens (i.e., cells capable of repopulating the tumor) have been killed, and that the number of such clonogens at the end of radiotherapy is Poisson distributed with a mean of $N\,S_{het}$, where N is the number of clonogens before treatment. The predicted TCP for the LQ model with heterogeneity is then given by the following expression:

$$TCP_{het} = exp[-NS_{het}] \quad (A5)$$

A.1.2. Linear quadratic linear (LQL) model

The Linear Quadratic Linear (LQL) [29,30] model was developed to modify the LQ model through the replacement of the continuously bending terminal part of the dose response curve for the logarithm of cell survival by the corresponding exponential cell inactivation mode. This was accomplished by modification of the "G-factor" which represents damage repair between radiation dose fractions. The resulting equation for the average number of lethal events per cell is as follows, where α, r and p_1 are adjustable parameters:

$$\alpha d + 2\alpha/r(p_1 d - 1 + exp[-p_1 d])/p_1^2 \quad (A6)$$

A.1.3. Universal survival curve (USC) model

In the USC model, the transition from curved to straight dose response for the logarithm of cell survival is done by introducing a cut-off or transition dose by means of the discontinuous, Heaviside step function. The resulting equation for the average number of lethal events per cell is:

$$\alpha d + \alpha d^2/r \text{ for } d \le r(1-\alpha p_1)/(2\alpha p_1), \text{ and}$$
$$d/p_1 - r(1-\alpha p_1)^2/(4\alpha p_1^2) \text{ for } d > r(1-\alpha p_1)/(2\alpha p_1) \quad (A7)$$

A.1.4. Pade linear quadratic (PLQ) model

In the PLQ model, the dose response shape is gradually altered, becoming less curved at high doses, by the presence of a term $1 + p_1\, d$ in the denominator of the function for the average number of lethal events per cell is:

$$(\alpha d + \alpha d^2/r)/(1 + p_1 d) \quad (A8)$$

A.1.5. Model parameters

Exploratory calculations using the LQ model with heterogeneous tumor cell radiosensitivity showed that increasing the initial number of tumor clonogenic cells (N) and/or decreasing the α/β ratio (r) generally decreased fit quality (increased the Akaike information criterion with sample size correction (AICc) [33,34]). Consequently, low values of N and high (effectively infinite) values of r were preferred in unrestricted fits, but sensitivity to these parameters was much lower than to α. To maintain biological plausibility and simplify the model, we restricted r to 10 Gy and N to 10^5 clonogens.

Eqs. (A6)–(A8) were used to calculate TCP for the LQL, PLQ and USC models in the same manner as described for the LQ model in Eq. (A5). Mathematically, this involved replacing the LQ model-based cell killing term $L_F = (\alpha\, d + \alpha r\, d^2)$ from Eq. (A1) with the corresponding term from the alternative model, where p_1 is an additional adjustable parameter (with different meaning and different units in each model). We applied the same parameter restrictions to these models as to the LQ model described above.

In the heterogeneous versions of each model, the shape parameter g for the Gamma probability distribution of α values is an additional adjustable parameter. Values of $2 < g < 6$ were preferred in unrestricted exploratory fits, but sensitivity to g in this range was much lower than to α. To maintain biological plausibility for the width of the distribution of α values, we restricted g to 5. The resulting distribution approximates a "bell-shaped" curve.

The only remaining parameter in the heterogeneous LQ model was therefore α, which could be interpreted as a measure of tumor radiosensitivity. We followed the same rationale for restricting parameters in alternative radiobiological models. The LQL, USC, and PLQ models each contain parameters analogous to β or to α/β from the LQ model. We restricted these analogous parameters to correspond to the condition $r = 10$ Gy. Parameter N was set to 10^5 for all models.

Consequently, the homogenous LQL, USC, and PLQ models each contained two adjustable parameters: α and a model-specific high-dose modification term (p_1). Heterogeneous versions of these models contained an extra parameter (g). Thus, for the purposes of calculating AICc scores, the total number of adjustable parameters was 2 for the LQL, PLQ, USC, and heterogeneous LQ models, and 3 for the heterogeneous LQL, PLQ, and USC models.

Exploratory calculations showed that the best fits (lowest AICc values) for all models to lung data were produced using isocentral SRT doses. For brain data the trend was reversed: peripheral doses produced better fits, but the difference in fits using peripheral or isocentral doses was not as great as for the lung. Consequently, we selected isocentral doses as the default for our analysis for both lung and brain data. The main conclusions (described below) were not changed if peripheral doses were used.

A.1.6. Exploration of heterogeneity using alternative models

An analytic solution was produced for the heterogeneous PLQ model, along the same lines as for the LQ model described above. For the heterogeneous LQL and USC models, numerical integration was necessary. In addition, we performed exploratory calculations using the same models, but assuming that the heterogeneity applies to radiosensitivity of tumors in different patients, rather than to the radiosensitivity of tumor cells within a patient. For this inter-tumor heterogeneity scenario, one exponentiation is carried inside the integral, which leads to the following equation:

$$TCP_{het(inter)} = \int_0^\infty PDF e^{-NS_{het}} da \quad (A9)$$

Eq. (A9) has no analytic solution and needed to be evaluated numerically for all models

Appendix B

B.1. Use of the akaike information criterion with correction for sample size (AICc)

AICc is rooted in information theory, and assesses how much Kullback–Leibler information is lost when each tested model is used to approximate the data. The model that loses the least amount of information relative to other compared models is considered the best. The equation for AICc is below, where LL is the log likelihood (the maximized value, produced by best-fit parameter values), q is the number of model parameters, and N_s is sample size (number of patients):

$$\text{AICc} = -2\text{LL} + 2q + 2q(q+1)/(Ns - q - 1) \quad (B10)$$

One of the most convenient features of using AICc is that it allows the evidence for multiple structurally distinct models to be compared. For example, consider $i = 1 \ldots n$ compared models. The relative likelihood of the (ith) model, called the evidence ratio ($E_{r(i)}$), can be expressed as:

$$E_r(i) = exp[-\Delta AICc_{(i)}/2], \text{ where } \Delta AICc_{(i)} = AICc_{(i)} - AICc_{(min)} \quad \text{(B11)}$$

Here $AICc_{min}$ is the lowest AICc value generated by the set of n models being compared. If $\Delta AICc_{(i)} > 6$, then the evidence ratio $E_{r(i)} < 0.05$, suggesting that the tested model has poor support from the data relative to the best-fitting model in the set of models being compared.

The Akaike weight, $w_{(i)}$, is another useful quantity – it represents the probability that the tested model would be considered the best-fitting model upon repeated sampling of the data. It is a normalized evidence ratio, i.e. the evidence ratio for the tested model divided by the sum of the evidence ratios for all the models being compared:

$$w_{(i)} = E_{r(i)} \Big/ \sum_{i=1}^{n} E_{r(i)} \quad \text{(B12)}$$

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