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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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