POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery

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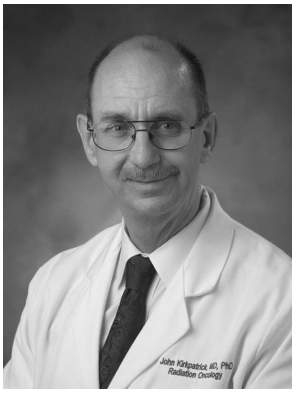
OVERVIEW

The linear-quadratic (LQ) model is frequently used for modeling the effects of radiotherapy at low and medium doses per fraction for which it appears to fit clinical data reasonably well. It has also been used at the very high doses per fraction encountered in stereotactic radiosurgery, but some have questioned such use because there are little clinical data to demonstrate that the model is accurate at such high doses. This is the proposition debated in this month's Point/Counterpoint.



Arguing for the Proposition is John P. Kirkpatrick, M.D., Ph.D. Dr. Kirkpatrick is an Associate Professor at the Department of Radiation Oncology, Duke University Medical Center. He has a Ph.D. in Chemical Engineering from Rice University, Houston, and an M.D. degree from the University of Texas Health Science Center, San Antonio, TX. His major research interests include treatment of tumors of the central nervous system, base of skull and spine, stereotactic brain and body radiosurgery, IMRT and other highly conformal techniques employing spatiotemporal optimization, tumor hypoxia, and quantitative modeling of the response of malignant and normal tissue to ionizing radiation.

Arguing against the Proposition is David J. Brenner, Ph.D., D.Sc. Dr. Brenner is a Professor of Radiation Oncology and Public Health at the Columbia University Medical Center. He focuses on developing models for the carcinogenic effects of ionizing radiation on living systems at the chromosomal, cellular, tissue, and organism levels. He divides his research time roughly equally between the effects of high doses of ionizing radiation (related to radiation therapy) and the effects of low doses of radiation (related to radiological, environmental, and occupational exposures). When not involved in radiation matters, he supports the Liverpool Football Club.

FOR THE PROPOSITION: John P. Kirkpatrick, M.D., Ph.D.

Opening Statement

The LQ equation is widely used to describe the effects of ionizing radiation on normal and neoplastic tissue.[1] In radiotherapy, we seek death of malignant cells and, more importantly, control/cure of disease while avoiding damage to the surrounding normal tissue. In conventionally fractionated ra-

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diotherapy, the LQ model is a useful tool to help predict isoeffects as a function of the total dose, dose/fraction, and treatment time.

In stereotactic radiosurgery, damage to the tumor is maximized and injury to normal tissues is minimized by administering high dose radiation—typically >12 Gy—to the tumor in a single fraction while limiting irradiation of adjacent tissue. At high doses per fraction, it is inappropriate to utilize the LQ equation because the model does not accurately explain clinical outcomes, is derived largely from *in vitro* observations, and does not consider the impact of radioresistant clonogen subpopulations.

Clinical outcomes from radiosurgery suggest that a single, high radiation dose is more efficacious than the "biologically equivalent" total dose calculated from the LQ model for conventionally fractionated radiotherapy.[2–4] For example, about 10% of patients with arteriovenous malformations (AVMs) treated to 42 Gy in 12 fractions (biologically equivalent to one 15 Gy fraction based on the LQ model with $\alpha/\beta = 3$ Gy) exhibited obliteration, and the rate of bleeding is not different than that in untreated patients.[4] In contrast, single fraction radiosurgery at 15 Gy yields an obliteration rate of about 50%.[5]

The discrepancy between clinical outcomes and predictions based primarily on *in vitro* cell survival curves may be related to radiation-induced changes in supporting tissue. Much of the data used to generate survival curves and estimate LQ model coefficients comes from *in vitro* cell culture experiments, typically at doses/fraction well below those used in radiosurgery. Preclinically, vascular endothelial damage appears to be triggered *in vivo* above 10 Gy/fraction.[6] Pathological studies of malignant and benign human brain lesions treated with radiosurgery show profound changes in the vasculature.[7,8] For example, for the treatment of AVMs, obliteration of abnormal vasculature and normal tissue damage are rare below 12 Gy but climb steeply above this dose threshold. Histopathological studies of AVMs show that the dominant damage following radiosurgery is loss of vascular endothelial cells, followed by obliteration of lumens.[7]

While the LQ model assumes an essentially homogeneous cell population, the tissue microenvironment is, in fact, quite heterogeneous. Local hypoxia is present in many tumors, significantly reducing radioresponsiveness of the overall tumor.[9] Moreover, tumors contain a subpopulation of cancer "stem cells" exhibiting enhanced repair of radiation damage, which may severely limit curability.[10] Neither heterogeneity of mechanism nor target population is reflected in the LQ model.

It is certainly possible to modify the LQ equation such that the model fits the dose-response curve and then rationalize that the addition of a new parameter reveals some fundamental mechanism.[1] However, one should not extend an empirical model outside the data set from which it has been derived. By truly understanding the underlying mechanism, we can create a robust model that both informs us clinically and aids us in formulating new therapeutic strategies.

AGAINST THE PROPOSITION: David J. Brenner, Ph.D., D.Sc.

Opening Statement

First, the standard LQ model is an approximation to more exact (but more complex) models. LQ generally works fine at doses per fraction below about 15–20 Gy. At higher doses per fraction, more exact versions of the LQ are available and can be used. Second, in order to use the standard LQ model to predict isoeffect tumor-control doses between high dose single fractions and multiple-fraction regimens, it is important to consider that reoxygenation will generally be different between the two cases. This can be taken into account with simple extensions to the LQ model.

1. High doses

It has long been known that the linear-quadratic model is an approximation to a wide range of damage-kinetic models, which describe the kinetics of DNA double-strand breaks (DSBs) and other basic lesions.[11] In such models, DSBs are resolved either through restitution or binary misrepair. At typical radiotherapeutic doses, most DSBs are removed by restitution, which results in the classic linear-quadratic dose dependence. At very high doses per fraction, binary misrepair can dominate, which results in a linear relation between effect and dose.[11] Overall, these mechanisms produce a linear-quadratic-linear dose-response relationship, as has been pointed out by many authors.[11–15]

In fact there have been detailed analyses, both experimental and theoretical, as to the doses below which the standard LQ approximation is reasonable to use. Experimentally, *in vivo* studies have suggested that the LQ works well up to about 20–24 Gy for a variety of murine end points,[1] and Garcia *et al.*[16] recently showed that *in vitro* cell survival followed the standard LQ up to about 15 Gy. Theoretically, Sachs *et al.*[11] estimated that the LQ approximation would be reasonable at doses below about 17 Gy and suggested practical corrections to the LQ model at somewhat higher doses. In practice, doses per fraction much above ~20 Gy are relatively unusual in radiosurgery, and so corrections to the LQ model in the relevant dose range are not major and are not hard to do.[11]

Of course one cannot rule out the possibility of other mechanisms, such as vascular endothelial damage contributing to radiation-induced tumor control. It is not yet clear how significant such mechanisms are in the clinic, but it is now clear that such effects are present at both low and high doses per fraction[17] and are not uniquely high-dose phenomena.

2. Reoxygenation

Almost all tumors have a hypoxic component, and one of the main motivations for fractionated radiotherapy is to permit reoxygenation between fractions. Clearly, this cannot happen with a single fraction, so if the goal is to produce isoeffect doses for tumor control between a single and a fractionated dose, one needs to model for reoxygenation. A simple modification to the LQ model that takes reoxygen-

ation into account is available for such calculations,[18] although the rationale for treating malignancies with a single fraction, and thus losing the benefits of reoxygenation, remains unclear.

Rebuttal: John P. Kirkpatrick, M.D., Ph.D.

The most important goal of modeling dose/response data is to predict clinical outcome. In conventionally fractionated radiotherapy, there is often a wealth of clinical data at the dose/fraction of interest and the clinician is justified in using the linear-quadratic model—or a modified form of this model—to *interpolate* response over a limited range. The prudent clinician, however, will exercise caution when radically altering a fraction scheme[19] no matter how compelling the radiobiological rationale.[20] In radiosurgery, clinical data are much more limited. Thus, "radiosurgeons" are faced with the task of *extrapolating* their clinical experience at low doses per fraction to the high-dose/fraction region utilizing a model with parameters largely derived from *in vitro* cell survival curves and small animal experiments.

Dr. Brenner argues that the *modified* linear-quadratic model provides a reasonable fit of isoeffect data up to about 20 Gy/fraction but, in most intracranial radiosurgeries, the maximum tumor dose is above 20 Gy. I will not argue with the complex mathematical formalisms and biophysics underlying these models, though one would be surprised if the modified models could not fit these data given the large number of adjustable parameters. However, as these data are typically based on cell-suspension experiments, they do not reflect changes at the tissue level which become more important as the dose/fraction increases.[21] Dr. Brenner alludes to "a simple modification to the LQ model" to account for reoxygenation but spatial/temporal variations in pO_2 in the tumor microenvironment are far more complex. And what about the effects of heterogeneous inherent radiosensitivity/repair, repopulation, and vascular endothelial damage (which is qualitatively different from the low dose response) at radiosurgical doses?[21–23]

Our present understanding of these mechanisms and their impact on tumor control and normal tissue complications at high doses/fraction is inadequate to model clinical isoeffects. Fortunately, our knowledge on these mechanisms is growing and it is incumbent on radiobiologists to incorporate this knowledge into models that not only predict clinical outcomes at elevated dose/fraction but also lead physicists and physicians to enhance treatment planning and biochemotherapies.

Rebuttal: David J. Brenner, Ph.D., D.Sc.

The heart of this debate can be summed up in Dr. Kirkpatrick's suggestion that LQ is merely an empirical, descriptive model. If this were so, one would indeed be very hesitant about using LQ as a guide for designing new protocols—the calamitous failure of the empirical NSD model comes to mind here.[24] But it was not so. In fact almost all mechanistically based radiobiological reaction-rate models reduce to the linear-quadratic model if the dose is not too high.[11] The LQ approximation to these radiobiological models is not merely some empirical power series expansion in dose; rather, it includes[11] the generalized Lea–Catcheside factor for protraction-based sparing,

$$G = (2/D^2)\int_{-\infty}^{\infty} R(t)dt \int_{-\infty}^{t} e^{-\lambda(t-t')}R(t')dt', \quad (1)$$

where $R(t)$ is the temporal dose distribution of the radiotherapy. Equation (1) provides a mechanistic description of the interaction of a DSB (or other primary lesion) made at time t', subject to first-order repair with rate constant λ, with another DSB made at a later time t—hardly the nonmechanistic empirical model that Dr. Kirkpatrick characterizes LQ to be.

As described above, LQ is indeed a lower dose ($\leq$15–20 Gy) approximation of more detailed mechanistic models, and these more detailed models can certainly be used if one is interested in effects at, say, 25–30 Gy/fraction.[11] But this procedure is certainly not the "extension of an empirical model" that Dr. Kirkpatrick suggests.

Dr. Kirkpatrick spends some time discussing AVM data. In fact a recent comprehensive analysis[25] of essentially all reported dose-response data for AVM obliteration, with doses per fraction ranging from 4 to 28 Gy, indicated that the data over the entire dose range were consistent with a standard sigmoidal LQ-based dose response, with an α/β value of about 2 Gy. No evidence here of different mechanisms at high versus low doses. Likewise the preponderance of evidence suggests that radiation-induced vascular endothelial damage to malignancies, while its clinical significance remains unclear, also occurs both at low and high doses.[17]

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