Modeling Clinical Radiation Responses in the IMRT Era

J L Schwartz[1], D Murray[2], R D Stewart[1] and M H Phillips[1]

[1]University of Washington Medical Center, Seattle, Washington, USA

[2]Cross Cancer Institute, Edmonton, Alberta, Canada

Abstract. The purpose of this review is to highlight the critical issues of radiobiological models, particularly as they apply to clinical radiation therapy. Developing models of radiation responses has a long history that continues to the present time. Many different models have been proposed, but in the field of radiation oncology, the linear-quadratic (LQ) model has had the most impact on the design of treatment protocols. Questions have been raised as to the value of the LQ model given that the biological assumption underlying it has been challenged by molecular analyses of cell and tissue responses to radiation. There are also questions as to use of the LQ model for hypofractionation, especially for high dose treatments using a single fraction. While the LQ model might over-estimate the effects of large radiation dose fractions, there is insufficient information to fully justify the adoption of alternative models. However, there is increasing evidence in the literature that non-targeted and other indirect effects of radiation sometimes produce substantial deviations from LQ-like dose-response curves. As preclinical and clinical hypofractionation studies accumulate, new or refined dose-response models that incorporate high-dose/fraction non-targeted and indirect effects may be required, but for now the LQ model remains a simple, useful tool to guide the design of treatment protocols.

1. Review

Radiation-induced toxicity in tumors and normal tissues arises from the interplay of multiple integrated pathways. Traditionally, our understanding of these pathways came from reductive methods where individual pathways were dissected and analyzed. The creation and testing of alternative and competing models that integrate multiple pathways is an important adjunct to mechanistic laboratory and preclinical studies of radiation response. The formulation of useful and parsimonious dose-response models at the multi-cellular or tissue level are also needed to guide the treatment planning process and for the retrospective analysis of clinical data. In practical terms, a parsimonious dose-response model is often the one that minimizes the number of adjustable (fitted) parameters.

Modeling radiation effects has a long history going back to target theory, developed by Lea in 1946 and published in 1955 [1], the linear-quadratic (LQ) model of Chadwick and Leenhouts [2] in 1974, and the dual action theory of Kellerer and Rossi [3] in 1978. These models were originally developed to help understand the nature of the initial radiation-induced molecular or cellular damage that leads to cytotoxicity, but none of these models fully account for the complexity and range of possible biological responses initiated by radiation-induced DNA damage [4, 5]. Neither do they consider the different modes of radiation-induced cell death [5]. New models of radiation responses that take into account some of our growing understanding about radiation-induced effects continue to be proposed

(see for example [6-8]). Most of these alternative and competing models often reduce to the LQ for low doses or low dose rates [9], which is surprising given the complexity of cellular radiation responses.

The LQ model often captures key aspects of how reproductive cell death changes with dose and only has two adjustable parameters (α and α/β). It continues to be a popular choice to design treatments and evaluate clinical outcomes. Perhaps the most often used LQ-based approach to estimate clinical radiation effectiveness is the calculation of Biologically Equivalent (or Effective) Dose (BED) [10]. BED is defined as $-\ln(S)/\alpha$, where S denotes the fraction of the cells that remain viable in the reproductive sense after treatment and α is the LQ model parameter related to the induction of lethal damage by individual radiation tracks. For a radiation treatment delivered as n daily fractions of size d (in Gy), the BED is:

$$\mathrm{BED} = nd[1+ d/(\alpha/\beta)]$$

Here, the LQ parameter α/β quantifies the overall sensitivity of a cell to changes in fraction size. Although estimates of α/β are sometimes derived from *in vitro* or *in vivo* studies, the most appropriate way to estimate α/β is to derive an estimate from clinical dose-response data. Regardless, estimates of α/β are specific to the normal tissue or tumor of interest. Historically, BED has mainly been used for designing and comparing treatments that vary in fraction number and/or the dose per fraction [10]. The advent and increasing use of hypofractionation with its short treatment courses, reduced fraction number and large dose per fraction (hypofractionation) has raised questions about the applicability of the LQ model and BED concept.

The hypothesized basis for the successful use of fractionation in radiation therapy is that fractionation provides time for repair of sublethal damage and tissue repopulation, thus reducing the impact of radiation dose in normal tissues while allowing for reoxygenation and reassortment in the cell cycle in tumor cells, both of which tend to increase tumor radiation sensitivity. Improvements in radiation targeting such as the use of SBRT (Stereotactic Body Radiation Therapy) now provide the opportunity to reduce the volume of normal tissue exposed to radiation, increase dose to tumors, and reduce fraction number. The ability to avoid critical normal tissue structures allows for the delivery of very high radiation doses to tumors in 1 or just a handful of fractions. A technical question that has arisen is whether traditional modeling with BED accurately predicts the clinical response to high dose/fraction and reduced fraction number.

It has been suggested that the LQ model tends to over-estimate BED when high dose fractions are used [11, 12]. The LQ model predicts a continuous bending down of the survival curve at high doses, while in vitro measurements indicate a linear-quadratic-linear (LQL) behavior, i.e., the cell killing is exponential for small and large doses and non-linear for intermediate doses. To address the issue of over-estimation of biological effects, modifications to traditional radiation models have been proposed. Guerrero and Li [11] used the lethal-potentially lethal (LPL) model proposed by Curtis [7] to motivate the derivation of a high-dose correction to the standard LQ model. Park et al. [12] proposed a hybridization of the LQ and target theory models to create a Universal Survival Curve (USC) model. Mehta et al. [13] did a comparative analysis of stage I non-small cell lung cancer treatments using BED and USC. The studies of Mehta et al. [13] included clinical data for both SBRT and 3-

dimensional conformal RT (3D-CRT), and fraction number ranged from 1 to more than 10. The authors reported that while BED was larger than the USC model for equivalent tumor control, the clinical significance of this difference for tumor control probabilities greater than 90% was minimal. Thus, while it is possible to account for the problem of BED over-estimation in the LQ model at high doses, the need for such corrections is so far not compelling, especially when one considers the additional fitted parameters introduced by other models. Future studies might lead to a change in this conclusion..

Another question that has been raised by hypofractionation studies is whether the excellent clinical outcomes associated with hypofractionation are due to the delivery of larger (biological) doses with SBRT or to new biology that becomes especially significant when the dose per fraction is large. Brown and colleagues [14] addressed this question in a discussion of the data presented in Mehta et al. [13]. They argued that the observed monotonic relationship between the tumor control probability and BED is consistent with dose escalation as the primary factor underlying the observed clinical responses; they found no difference in tumor control for single fraction SBRT, multifraction SBRT or 3D-CRT for treatments that deliver the same BED.

In contrast to the observations of Mehta et al. [13] and Brown et al. [14], Zelefsky et al. [15] reported on tumor local progression-free outcomes after treatment with single-dose or hypofractionated regimens for extracranial metastases from renal cell primary tumors. The authors reported 3-year progression-free survival rates of 88% for single doses greater than 24 Gy and 17% for hypofractionated doses (total doses ranged from 20 Gy to 60 Gy). In this example, BED for the single-dose treatment was much less than BED for hypofractionation. Single doses less than 24 Gy (18-22 Gy) had much lower 3-year survival rates (21%) than that observed for the 24 Gy single dose (88%), suggesting a dose threshold for some radiation effect that influences this clinical endpoint. The work from Zelefsky, Fuks, Kolesnick, and colleagues [16-18, 15] suggests that, at least in their clinical model, the biological mechanisms underpinning low dose radiation effects, i.e., the dose range in which target theory and the LQ model are most appropriate (accurate), may differ in substantial ways from high dose biology mechanisms.

Target theory and the LQ model are largely premised on the hypothesis that only those cells that are directly irradiated (damaged) by radiation manifest a response. However, there is growing evidence that non-targeted and indirect effects may play an important role in high dose tumor biology [19-23]. Moreover, the non-targeted and indirect effects of radiation do not necessarily show the same dose response characteristics traditionally observed in cell survival experiments.

Effects on tumor microvasculature and immune responses following radiation exposure are two examples of indirect effects that might not be explained by BED. Fuks, Kolesnick, and colleagues [16-18] emphasize the importance of ceramide-mediated endothelial cell apoptosis of tumor microvasculature as an indirect regulator of radiation-induced tumor cell toxicity that might account for the apparent dose threshold reported in Zelefsky et al. [15].

Abscopal effects, where significant tissue responses are observed at sites far from the radiation-targeted tumor, are another type of indirect radiation effect. Abscopal effects have been associated with immune response stimulation [24-28]. In fact, immune response is important for local control following radiation exposure. Stone et al. [29] reported many

years ago that the dose needed to control tumors (TCD50) was twice as high in mouse models that lack T cells. Demaria, Formenti and their colleagues have published extensively on the role of radiation as an immunological adjuvant [30, 24, 31, 5]. In their studies, combining radiation treatment of one tumor with anti-CTLA-4 antibody to overcome T cell tolerance led to significant growth inhibition both in the irradiated tumor and a distant unirradiated tumor [24]. In a review of the importance of dose and fractionation on immune response, Demaria and Formenti [30] reported that single doses of radiation can induce an antitumor immune response in a dose-dependent manner, but there is no consensus yet on the shape of the dose response or type of cell inactivation mechanism required for that stimulation. As for fractionation, while Dewan et al. [24] reported that fractionation was more effective than single doses in inducing the immune-mediated abscopal effect, in their review on this subject, Demaria and Formenti [30] note that other investigators find that single doses are more effective than fractionated doses. Use of different tumor models might explain the discrepancies between different publications in terms of dose and fractionation dependence of immune stimulation. What is important for this discussion is that the immune stimulation is a non-targeted, indirect effect of radiation that is unlikely to show an LQ dose response.

2. Conclusion

It is important to remember that target theory and the LQ model ultimately provide descriptions of phenomena rather than an explicit model of specific biological mechanisms or pathways. As operational tools, they are useful models to guide and compare the effects of fractionated radiation treatments. Because of technological improvements in our ability to deliver highly conformal doses to tumor targets while minimizing the dose to normal tissue, it appears likely that radiation oncology is rapidly moving towards the use of treatments delivered in a single or a few fractions. Although the LQ is likely to remain a useful model for the analysis of clinical outcomes and for guiding the refinement of treatment protocols, caution needs to be exercised in the application of the LQ to large dose per fraction treatments. In particular, there is increasing evidence that the success of high dose per fraction treatments may be due more to non-targeted or indirect radiation effects than to classic radiobiological mechanisms motivating the LQ and target theory. It can be argued that, when applied to clinical data, the LQ implicitly includes some of the indirect effects of radiation. If the LQ model fits the clinical data as suggested [14], it is possible to claim that all of the relevant mechanisms underlying the clinical observation are included (implicitly) in the model. Additional laboratory and preclinical studies are needed to test this hypothesis.

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4. References

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