

EDITORIAL

WE FORGET AT OUR PERIL THE LESSONS BUILT INTO THE  $\alpha/\beta$  MODEL

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Dr. Glatstein's recent Editorial, "The Omega on Alpha and Beta" provided a thoughtful, provocative, and skeptical view regarding the utility of the linear-quadratic (LQ) model in radiotherapy (1). By contrast, we suggest that, over the past quarter century, the use of  $\alpha/\beta$  ratios in the context of the LQ model has markedly improved our understanding of one of the most basic tools that radiation oncologists have at their disposal: the potential to optimize fractionation. We do not doubt Dr. Glatstein's suggestion that one can indeed be an excellent clinical radiation oncologist without "knowing squat about  $\alpha/\beta$ " ratios. We do, however, suggest that the LQ model continues to provide our field with two important tools. First, with appropriate caveats, LQ is an important tool for the research-oriented radiation oncologist wishing to design improved radiotherapeutic protocols. However, beyond this, we also suggest that the LQ model provides our field with ongoing easily digestible lessons about the clinical significance of fractionation and overall time—lessons that can often get lost in the enthusiasm for new irradiation technologies.

It has been well established since the 1930s that fractionation is a key determinant of radiotherapeutic response (2); however, until the 1980s, we did not have a reliable quantitative framework to use this insight to generate improved protocols. What we had were empirical formulae such as the NSD, CRE and TDF (Nominal Standard Dose, Cumulative Radiation Effect and Time-Dose Factor [2]), which summarized past clinical experience. However, when these were used to design protocols with very different fractionation schemes from those on which they were based, the results were sometimes disastrous (3–5).

By the early 1980s came the application of the LQ  $\alpha/\beta$  formalism to clinical radiotherapy, initially by the Houston (6) and Amsterdam (7) groups. Essentially this provided a formalism that quantified the changes in the response of

early-responding tissues, including tumors, and late-responding sequelae, when the fractionation pattern (and, subsequently, the overall time [8]) was changed. The LQ formalism is a consequence of the repair/misrepair kinetics of radiation-induced damage (9); by the 1980s, it was already a well-studied mechanistically based model of dose and dose–rate response in laboratory settings, but the insight of the Houston and Amsterdam groups was to see that by using clinically derived parameters, the model could be applied in the clinic. Both groups showed that the LQ model parameter  $\alpha/\beta$  provided a quantification of the fractionation response; thus, the already established qualitative differences in fractionation response between early- and late-responding tissues (10) could be quantified through differences in this  $\alpha/\beta$  ratio. So in its clinical context, the LQ model became, and still is, a mechanistically based formalism but with parameters directly derived from clinical data (2).

The key here is that the LQ formalism has worked. Over the past two decades, dozens of new radiotherapeutic protocols have been designed using the LQ formalism with  $\alpha/\beta$  parameter values derived from clinical data, and we have not had any of the clinical disasters that were associated with the application of empirical formulae such as NSD. Alternative fractionation schemes designed using the LQ approach have not only shown clear survival benefit (11), but have also come out very much as predicted by the LQ modeling using clinical  $\alpha/\beta$  parameters, even for highly nonstandard protocols such as hyperfractionation (12), high-dose-rate vs. low-dose-rate brachytherapy (13), or prostate hypofractionation (14).

We suspect that the perceived "trouble with  $\alpha/\beta$  ratios" (1) stems from three main concerns:

1. That it is inappropriate to derive  $\alpha/\beta$  values from *in vitro* laboratory-based systems, in that no single *in vitro* assay

could reflect the multitude of mechanisms that lead, particularly, to late sequelae. We would agree with this concern if that was indeed how  $\alpha/\beta$  values for late-responding tissues were routinely estimated. However, they are almost always estimated by an analysis of clinical data (2, 15), and thus the dominant processes are effectively “built in” to the  $\alpha/\beta$  estimates.

2. That, because radiation-induced late effects are not wholly attributable to cell killing (and indeed radiation-induced nonlethal cellular dysfunction is clearly an important mechanism here (16)), this might invalidate the use of the LQ model. However, it has long been established that radiation-induced nonlethal mutation yields also typically follow the standard LQ formalism at radiotherapeutic doses (17).
3. That estimated  $\alpha/\beta$  values represent averages over many patients. This is certainly true, but then the same applies to all radiotherapy treatment protocols—and the possibility of assessing individualized  $\alpha/\beta$  values represents just one of the directions that might be possible in the future for individualized predictive assays.

Quite conspicuous by their absence in Dr. Glatstein’s critique (1), or indeed elsewhere, are specific suggestions for alternatives. Unless we think our field has progressed just about as far as it can go, we need to take advantage of the rapidly developing technologies for targeting and timing; thus, some practical and reliable tool is needed to design and assess potential new fractionation protocols. The LQ model with clinically derived  $\alpha/\beta$  values represents the simplest reliable mechanistically based quantitative description of how different tumors, different early-responding tissues, and different late-responding normal tissues respond to changes in fractionation and overall time (6–8). It represents a tractable mechanistic model that is

nevertheless anchored in clinical experience through clinically derived  $\alpha/\beta$  ratios.

It should be emphasized that the clinical application of LQ is not for generating absolute *ab initio* predictions of radiotherapeutic response, but rather to compare one fractionation/protraction protocol with another. When two fractionation schemes being compared each contain more than just a few fractions, their differences are expected to be dominated by repair and repopulation, and here the standard LQ model (6–8) would be expected to perform well. For comparative studies involving more “extreme” protocols, such as a single very high-dose fraction, the standard LQ model undoubtedly becomes less reliable (18). Modifications of the LQ model for such situations do exist (19, 20), although at the price of increased model complexity and consequent decreased practical usability.

When used with appropriate caution, the LQ model has proved a very useful tool for designing and comparing the effects of new fractionation protocols. More than that, built into the LQ model with its clinically derived parameters, are key lessons about fractionation and overall time, learnt over many decades and at considerable cost to many patients, and that are likely to be forgotten if designers of new radiotherapy protocols do not appreciate the significance of clinical  $\alpha/\beta$  parameters. A pertinent example is the growing trend toward the use of hypofractionation. There are specific biologic situations when hypofractionation makes sense relative to more standard protocols (21, 22); in general, however, the LQ model provides explicit quantitative predictions of increased sequelae when the number of fractions is markedly reduced, particularly when critical normal tissues are too close (23–25) to the target volume. We forget at our peril the lessons built into the  $\alpha/\beta$  model.

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