Editorial

The Power of Radiation Biophysics—Let’s Use It

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Two recent editorials in this Journal about the linear quadratic (LQ) model (1, 2) have debated its use on essentially empirical grounds. Missing are its roots in biophysics and what they state about how it can (and cannot) be used. In the 1970s, 2 roads led to analysis of in vitro cell killing by ionizing radiation in terms of the underlying mechanisms. Kellerer and Rossi (3) explored the statistics of energy deposition in small volumes—the microdosimetric approach. Chadwick and Leenhouts (4) related cell killing to lesions in 2-stranded DNA—the biophysical approach. Both approaches postulate that radiation can kill cells by 2 distinct processes, a 1-hit mechanism and another that requires 2 independent events. We began to use the LQ equation in 1973 for the pragmatic reason that it fits the survival data better than the other models we tested (5). It soon emerged that, if key factors were controlled, this equation offers insights into the mechanisms involved in cell death and survival during and after irradiation. Here, we reviewed 4 forms of this equation that describe cell survival in specific circumstances and how they might help those working to improve radiotherapeutic protocols.

The basic LQ equation states that the cell surviving fraction (S) is the product of 2 Poisson escape probabilities. The mean numbers of events for the underlying mechanisms are proportional to the first and second powers of dose, D, respectively.

\[
S = \exp(-\alpha D) \times \exp(-\beta D^2) \quad \text{LQ (1)}
\]

The sublesions associated with \(\beta_D\)-inactivation (likely single-strand breaks [6]) repair rapidly at mammalian body temperatures. Thus, to obtain precise values of \(\alpha\) and \(\beta_D\), cells are irradiated at dose rates >10 Gy/min or at 2°C-6°C, such that the first sublesion of a 2-hit event will not be removed before a second has been induced. The sources available to most radiobiology research have dose rates of 1-2 Gy/min at positions convenient for cell irradiation; thus, low temperatures should be used to obtain the maximal and true value of \(\beta_D\). This basic LQ equation can be written in a form that yields a straight line such that the 2 parameters are the intercept at 0 dose and the slope, respectively.

\[
\frac{-\ln(S)}{D} = \alpha + \beta D \quad \text{LQ (1a)}
\]

The basic LQ equation applies to cell populations of sufficiently homogeneous radiosensitivity. Thus, much of our research investigated the cell-survival and cell-killing mechanisms with synchronized cells in mitosis (tetraploid) or in G1 phase (diploid) of the cell cycle. Stationary (Go) phase cells (diploid) were also used in experiments in which it was not feasible to synchronize the cells. In this model, the \(\alpha/\beta\) ratio defines the dose at which the different mechanisms contribute equally to cell killing.

However, most radiobiology research uses asynchronous populations of normal or tumor cell lines whose survival can also be characterized with an LQ equation. Although LQ Eq. 1 can be fitted to such data, the resultant \(\alpha\) and \(\beta\) parameters do not precisely express the underlying mechanisms. Rather, they are associations of values for subpopulations in which the range of \(\alpha\) values affects the fitted \(\beta\) values and vice versa (5). This is reflected by a different form of the equation:

\[
S = \exp(-\alpha x D) \times \exp(-\beta_D x D^2) = \sum x \exp(-\alpha x D) \times \exp(-\beta_D x D^2) \quad \text{LQ (2)}
\]

where \(n_x\) is the fraction of cell population \(x\), with parameters \(\alpha_x\) and \(\beta_D\), and \(\bar{\alpha}\) and \(\bar{\beta}_D\) are effective values for the mixed population. The mechanistic ambiguity of the parameter values from mixtures of cells of different radiosensitivity should be clear. This form of the equation will be useful for asynchronous cell populations, for mixtures of oxygenated and hypoxic cells, for mixtures of quiescent and proliferating cells, for cells in planning tumor volume voxels exposed to particles of the variable linear energy transfer, and so forth. The variation in \(\bar{\alpha}\) for various human

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tumor cell lines correlates well with the different radioresponses of the tumors from which they were derived; in contrast, $\sqrt{\beta_0}$ varies only slightly among cell types (7, 8).

Cell killing by radiation was also characterized at intermediate dose rates and different temperatures. These studies identified a first-order repair process that accounts for the reduced cell inactivation observed (9). This effect can be expressed in another form of the basic equation:

$$S = \exp(-\alpha D) \times \exp(-\beta_0 D^2 \left(1 - \frac{1 - \exp(-m)}{m}\right)/m)$$

LQ (3)

where $\alpha$ and $\beta_0$ are unchanged, $m$ is the ratio $kD/R$, $k$ is the measured rate constant for repair of sublesions at the specific temperature of interest, and $R$ is dose rate. This form of the equation should be used when low dose rates or prolonged exposures are used. It tends toward a straight line at a high dose on a semi-log plot. Our studies yielded a value of $k = 0.03/$min at $37^\circ$C for Chinese hamster fibroblasts (9); however, human tumor cell lines might have different repair rates. Nevertheless, this form of the equation quantitatively expresses the reduced cell killing due to repair of sublesions during exposure of more than a few minutes, which should come as no surprise. Additional research might indicate that an additional and much slower first-order repair process, such as is observed for single-strand break repair (6), might result in reduced cell killing at low dose rates.

Those working to introduce radiobiology parameters into treatment planning protocols need another form of the basic equation. Because most radiation therapy is delivered in daily fractions, 5 d/wk, there is enough time between dose fractions for complete repair of the sublethal damage associated with the 2-hit mechanism and for clonogen reassortment. Thus, fractionated doses will produce cell killing, as described by the following equation:

$$S = \exp\left[-n(\alpha_d + \beta_d d^2)\right]$$

LQ (4)

where $n$ fractions of dose $d$ deliver a total dose $D = nd$. On a plot of log(S) vs $D$, these survival curves also take on a linear appearance over several decades of cell kill (10).

If one knows the total number and the intrinsic radiosensitivity of clonogens in a group of similar tumors, the tumor control probability models can predict local tumor control as a function of the total dose. The radiation inactivation parameters for pathologically similar tumors in different patients or for clonogens in individual tumors are known to vary (11). Consequently, guesstimates are made for specific tumor-treatment cases and controversy can ensue. A case in point, the analysis of prostate cancer brachytherapy yielded excellent results when a very low value for $\alpha$ (0.036 Gy$^{-1}$) and 15 ± 2 clonogens were assumed for tumors with Gleason scores of mainly 6 and 7 (12). Several pathologists and urologists consider this clonogen number to be low for tumors of this volume. Equally good fits to these clinical data were obtained using average values of $\alpha$ and $\beta$ for prostate cancer cell lines reported in published studies, with clonogen numbers of 1-10 million and the recently obtained knowledge of severe hypoxia in some human prostate cancers (10). That such widely disparate values can produce equally good fits to clinical data underlines the need for better tumor biology information. Additional studies could fine tune the more important parameters such as $\alpha$ and $\beta$, with some estimate of errors, quiescent vs. proliferating compartments, oxygenated vs hypoxic cells, sublethal damage repair rates, and clonogen number.

With realistic parameters, radiation oncology could go beyond empiricism to tumor control probability modeling to predict confidently the relative merits of fractionation schemes and to better understand the 4 or 5 Rs of radiobiology that apply to tumor radiation therapy (13, 14).

As for normal tissue complication probability modeling, even less is known of the underlying mechanisms of normal tissue damage that account for deleterious effects of radiation. If the damage results from killing stem cells in the tissue, for example, quantitative LQ radiobiology could come into play. However, when the late effects of radiation involve interactions between stem cell, stromal, and vascular elements in the tissues, it is unclear how the LQ analyses might apply.

Most current radiobiologic research does not attempt to meet the conditions for LQ analysis and thus does not readily relate to underlying physical mechanisms. Our research has suggested that single-hit inactivation by X-rays results from electron track ends depositing energy in compacted chromatin (with some indication of a lipid/DNA composition), producing nonreparable lesions (15). However, 2-hit inactivation results from simple DNA lesions (mostly reparable strand breaks) produced by simple ionizations (~60 eV), those that radiation chemists term “spurs.” Hydroxyl radicals generated in cellular water mediate a large proportion of the killing of cells by both mechanisms (9). How these different lesions can produce the aberrations observed in the mitotic chromosomes of irradiated cells has been elegantly described (16).

Using the appropriate LQ equation, this biophysical understanding of tumor cell killing by ionizing radiation can be extremely useful in the design of improved treatment protocols. For example, hypofractionated radiation therapy causes less stress to the patient (shorter overall treatment times) and has lower cost (fewer patient setups) and thus should be studied vigorously. Current treatments with 1.8-2.0 Gy/fraction were optimized empirically using inferior imaging and radiation delivery technologies. Because the 2 cell-killing mechanisms exhibit entirely different properties (8), LQ analysis can be used to usefully guide adjustments to current protocols in light of the expected biologic consequences. The previous radiation biophysical studies of tumor cell killing should be embraced and the appropriate LQ equations exploited for the design of improved treatment strategies.

References