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The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

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The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanistically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.
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Let us start from the premise that we need some model for calculating isoeffect doses when alternate fractionation schemes are considered. In addition, apart from increasing interest in alternative fractionation/protraction schemes, it is essential that we know how to compensate appropriately for missed radiotherapy treatments.

The tool most commonly used for quantitative predictions of dose/fractionation dependencies is the linear-quadratic (LQ) formalism.[1-5] In radiotherapeutic applications, the LQ formalism is now almost universally used for calculating isoeffect doses for different fractionation/protraction schemes.

In contrast to earlier methodologies, such as cumulative radiation effect, nominal standard dose, and time-dose factor,[6,7] which were essentially empirical descriptions of past clinical data, the LQ formalism has become the preferred tool largely because it has a somewhat more biological basis, with tumor control and normal tissue complications specifically attributed to cell killing. By contrast, descriptive empirical models can go disastrously wrong if used outside the dose/fractionation range from which they were derived, as when NSD was applied to large doses per fraction.[8,9]

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Mechanistic Background to the LQ Model

It is clear that radiotherapeutic response, both for tumor control and for complications, is dominated by cell killing,[2,10,11] and LQ is a mechanistic model of cell killing. Underlying the application of LQ to fractionation/protraction effects is pairwise misrepair of primary lesions such as double-strand breaks (DSBs) or base damage (hereon in we shall refer to DSB as the primary lesion, but base damage sites may well also be relevant here[12]). As schematized in Figure 1, cell killing occurs via chromosome aberrations such as dicentric aberrations,[13] which are formed when pairs of nearby DSB wrongly rejoin to one another.[14] Protracting the exposure time potentially allows the first DSB to be repaired before the second is produced, and the LQ approach quantifies this effect.[5] Nowadays, this binary DSB misrepair model is the most usual way to motivate the standard LQ approach, but different biological rationales for the same mathematical formalism have also been given, as we will discuss.

It is important to stress here that the standard LQ formalism, as applied to time-dose relationships, is not merely a truncated power series in dose. Its key feature here is a specific mechanistically based functional form for the protrac-

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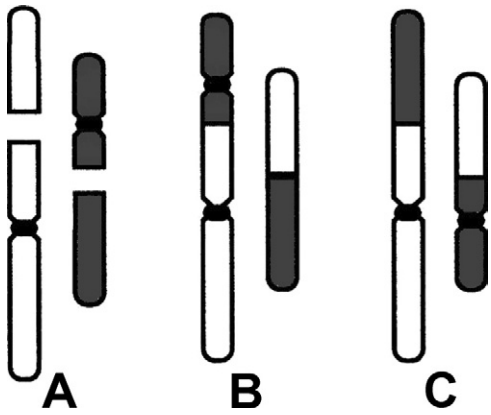

Figure 1 Examples of binary misrepair. Figure 1A shows 2 chromosomes; each has 1 DSB, shown as a gap. Centromeres, which are needed for proper transmission of chromosomes to daughter cells at mitosis, are shown as black constrictions. Most DSBs are correctly restituted, but a few undergo binary misrepair. As shown in Figure 1B, binary misrepair can result in a dicentric chromosome aberration, which generally destroys the clonogenic viability of the cell. In about half the binary misrepair events, the 2 DSB shown in Figure 1A lead to a translocation, shown in Figure 1C; translocations involve large-scale rearrangements and can cause potentially precarcinogenic alterations in cellular phenotype, but most do not impair cellular survival.

tion factor, usually designated by G, which takes into account dose protraction or fractionation. Expressions for special cases of the time factor, G, were derived by Lea and Catcheside[4,15]; a general form was subsequently derived[16] and has since been rederived from several different points of view.[9] We refer to this general form of the time factor, given explicitly in equation 4 shown later, as the generalized Lea-Catcheside time factor, G.

The LQ Formalism

The LQ model, in its most usual current version, describes cell killing in terms of the following mechanisms:

1. Radiation produces DNA DSBs proportionate to the dose.
2. These DSB can be repaired, with the first-order rate constant λ ($= ln\ 2/T_{½}$, where $T_{½}$ is the repair half time). In practice, there may be more than 1 class of DSB that may be repaired with different rate constants; the LQ formalism can be simply extended to take this into account.
3. In competition with DSB repair, binary misrepair of pairs of DSBs produced from different radiation tracks (ie, different photons) can produce lethal lesions (often identified as predominantly dicentric chromosomal aberrations), the yield being proportional to the square of the dose (see the quadratic term in equations 1 and 3). The 2 independent radiation tracks can occur at different times during the overall regimen, allowing repair of the first DSB to take place before it can undergo pairwise misrepair with the second; it is this phenomenon that is the heart of the fractionation/protraction dependence in the LQ formalism.
4. In addition, single radiation tracks can produce lethal lesions, possibly by a variety of mechanisms, the yield being linearly proportional to the dose.

Overall, in the LQ formalism, the yield (Y) of lethal lesions and the corresponding survival (S) equation are

$$Y \propto \alpha D + G\beta D^2 \quad (1)$$

(note that the biologically effective dose, BED, is defined as Y/α [1]). Then, assuming the lethal lesions are Poisson distributed from cell to cell, the surviving fraction will be

$$S = exp(-Y), \quad (2)$$

and thus

$$S = exp(-[\alpha D + G\beta D^2]). \quad (3)$$

In equations 1 and 3, G is the generalized Lea-Catcheside time factor, which accounts quantitatively for fractionation/protraction; it is important to note that G acts only on the quadratic component, as described in point 3 above. The generalized time factor has the form[16]

$$G = (2/D^2)\int_{-\infty}^{\infty} \dot{D}(t)dt \int_{-\infty}^{t} e^{-\lambda(t-t')}\dot{D}(t')dt'. \quad (4)$$

Here $\dot{D}(t)$ describes the variation in dose rate over the entire course of the radiotherapy, and λ is a characteristic damage repair rate. Generically, the term after the second integral sign refers to the first of a pair of DSBs required to produce a lethal lesion, the exponential term describing the reduction in numbers of such DSB through repair; similarly, the term after the first integral sign refers to the second DSB, which can interact with DSBs produced earlier that still remain after repair.

The time factor, G, can be calculated for any fractionation/protraction scheme and systematically accounts for the effects of protracting the dose delivery in any way. G can take values from 0 to 1, with $G = 1$ for a single acute dose, leading to the simplest single-fraction LQ formalism:

$$S = exp[-(\alpha D + \beta D^2)]. \quad (5)$$

The interpretation of $G < 1$ is a reduction in cell killing because of repair that occurs during protracted radiotherapy. Two examples show the main features of the general expression for G. For irradiation with n short fractions, each separated by a time T[17]:

$$G = [2\theta/(1-\theta)]\ [n - (1-\theta^n)/(1-\theta)] \quad (6)$$

where $\theta = exp(-\lambda T)$. When the time between the short fractions is very long, then

$$G = 1/n, \quad (7)$$

and the most simple LQ model for well-separated fractionated exposures become

$$S = exp[-D(\alpha + \beta D/n)]. \quad (8)$$

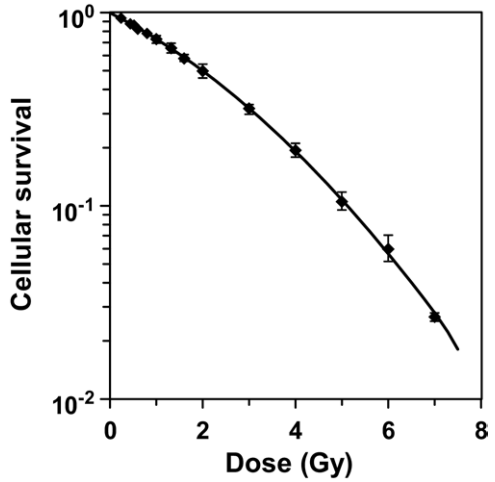

Figure 2 Survival of x-irradiated CHO cells, determined by flow cytometry population counting, 5 days after treatment.[22] The curve is the corresponding LQ model fit.

Different fractionation/protraction schemes have different time factors, G, any of which can be calculated[3,18] from equation 4.

Does the LQ Model Predict the Variation of Effect With Dose in the 2-Gy to 18-Gy Dose per Fraction Range?

The goal here is to be able to make equieffect regimen extrapolations from standard regimens, typically with 1.8 to 2 Gy per fraction, to hypofractionated regimens. Possible hypofractionated doses per fraction are, for example, up to about 7 Gy for prostate[19] and up to about 15 Gy for non–small-cell lung cancer.[20] For fractionated stereotactic radiotherapy, we are interested in extrapolating in the opposite direction, from single-fraction doses as high as 18 Gy, to hypofractionated exposures with lower doses per fraction.[21]

So the general question is whether the LQ formalism described in the previous section describes radiotherapeutically relevant dose responses in the dose per fraction range from, say, 2 Gy to 18 Gy. For many situations, such as prostate cancer hypofractionation, the dose per fraction range of interest is probably about 2 to 7 Gy.

We shall first discuss some in vitro and in vivo experimental data to address the question and then discuss some alternate mechanistic models to the LQ equations and their potential impact, relative to LQ-based predictions.

In Vitro

It is not easy to generate precise, accurate measurements of cell survival at high radiation doses. One recent approach to this problem is to use DNA flow cytometry for counting cell numbers rather than colonies. This approach can produce very high statistics data and establish precise survival curves. Figure 2 shows such survival data for irradiated Chinese hamster ovary (CHO) cells,[22] where it can be seen that the standard errors can be made very small with this approach. The single-fraction LQ-model fit (equation 5) to these data clearly fits very well, indicating that it can predict the pattern of dose responses over the key 2- to 7-Gy dose range.

Similar results have recently been reported by Garcia et al[23] using a more standard colony assay to measure cell survival. In this case, surviving fractions in the dose range from 0 to 16 Gy were measured. To estimate dose regions in which the single-fraction LQ model (equation 5) did/did not fit the data, the authors fitted the data from 0 Gy to 4 Gy and then from 0 Gy to progressively larger doses, each time assessing the goodness of fit of the model to the data. Typical results are shown in Figure 3, where it can be seen that the quality of fit to the LQ model does not decline significantly until doses above 15 Gy are included.

In Vivo

There is a fairly wide range of quantitative in vivo endpoints for which it is possible to test concordance with the LQ predictions in the 2- to 20-Gy range.[24] Figure 4, for example, shows some isoeffect results from Van der Kogel[25] for late-responding damage to the rat spinal cord, from Douglas and Fowler[26] for acute damage in mouse skin, and from Peck and Gibbs[27] for early and late damage to the murine small intestine. The form of the plot, the so-called reciprocal-dose F_e plot,[24,26] is such that, if the LQ formalism applies, the data would fall on a straight line. Although the reciprocal-dose plot approach is not an optimal methodology for parameter estimation,[28,29] it does provide a visual indication of how well in vivo data agree with the LQ model in the dose range of interest. All the quantitative in vivo endpoints in Figure 4 are consistent with the LQ model over a wide range of doses per fraction, including those of interest in hypofractionation. Extensive F_e plot analyses by Barendsen,[24] using 12 normal tissue response endpoints, reached the same conclusion. Although more sophisticated methods are available for assess-

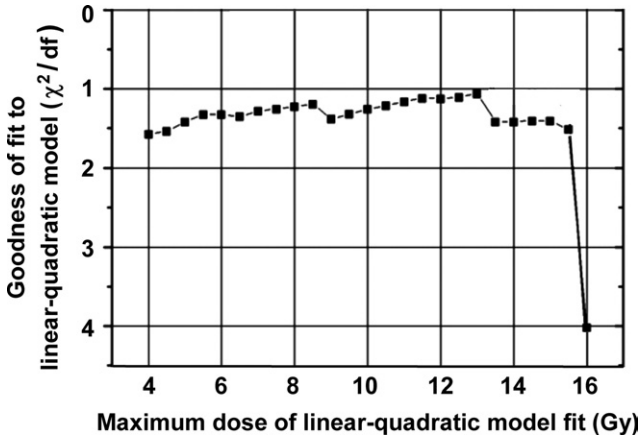

Figure 3 Goodness of fit of LQ model to measured cell-survival data as a function of the dose range that was fitted.[23] The quantity plotted is χ^2 per degree of freedom; hence, smaller values represent better fits to the LQ model. For example, the left-most point represents a good fit of the LQ model to cell-survival data in the dose range from 0 Gy to 4 Gy, and the right-most point represents a less good fit of the LQ model to cell-survival data in the dose range from 0 Gy to 16 Gy.

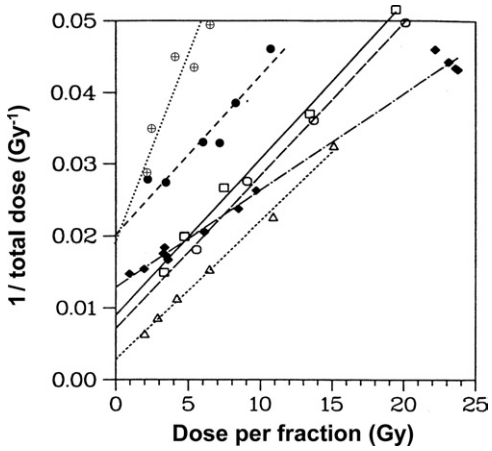

Figure 4 Isoeffect data for late response from 3 (□ O Δ) different regions of the rat spinal cord,[25] for acute skin reactions (♦) in mice,[26] and for early (●) and late (⊕) murine intestinal damage.[27] The data are plotted in a "reciprocal-dose F_e" form[26] such that, if they follow an LQ relationship, the points fall on a straight line.

ing agreement with the LQ model,[30], given the inherent uncertainties in the data, it is clear that all these data, including those for single fractions of ~20 Gy, are consistent with the LQ model.

Is the LQ Model Correct?

We have shown that the LQ model is reasonably predictive of dose-response relations, both in vitro and in vivo, in the dose per fraction range of 2 to 15 Gy. Of course, it goes without saying that no mechanistic model describing dose-time patterns can be fully complete or correct so we discuss here some of the main mechanistic uncertainties associated with the LQ model.

Pairwise Production of Chromosome Aberrations Is Not the Only Mechanism Mediating Cell Killing

Again, it is argued that cell killing is the dominant process mediating radiotherapeutic response,[2,10,11] both for early and late effects, including vascular effects. But not all cell killing is mediated through chromosome aberrations produced by pairwise misrepair. However, other cell-killing mechanisms, such as apoptosis and induction of small mutations, are dose rate independent.[31] LQ incorporates both dose-rate–independent mechanisms such as these (in the linear term), and dose-rate–dependent mechanisms (in the quadratic term). Assuming LQ correctly models the mechanisms involved in the dose-rate–dependent term, then with appropriate parameters (α/β actually is the ratio of the dose rate independent to the dose-rate–dependent term) LQ should be adequate for predicting fractionation/protraction effects.

There Are Other Mechanistic Models Describing Pairwise Production of Chromosome Aberrations as Well as LQ

It has been known for some time that, in addition to the LQ model, various other binary misrepair models lead to the same generalized Lea-Catcheside time factor, G, in an appropriate approximation and thus predict virtually the same time-dose relations as does the LQ approach. This result was shown by several authors[17,32-35] for the repair-misrepair model,[36] the lethal–potentially lethal model[33], and more general binary misrepair models. In light of the conceptual similarities between the LQ model and other binary misrepair models, the fact that the corresponding formalisms make virtually equivalent predictions for dose-time relationships is not, in retrospect, particularly surprising.

Lethal Lesions Are Not Poisson Distributed From Cell to Cell

This Poisson assumption, embodied in equation 2, is used in all models that calculate the fraction of inactivated cells from the average yield of lethal lesions. It is certainly the case that, based on microdosimetric considerations, this distribution is not exactly Poisson.[37] For densely ionizing radiations such as heavy ions or neutrons, this point is well taken and important. But, for sparsely ionizing radiation such as x or γ rays below ~50 Gy per fraction, deviations from a Poisson distribution are quite minor.[5,38]

Repair Mechanisms Saturate at High Doses

Various high-dose saturable repair (SR) models have been considered,[39-43] all having in common the notion that the per-lesion repair rate decreases as the dose- and the production of initial damage-increase. This might arise, for example, if repair enzymes can be overloaded. Such a change in repair rates with increasing doses might in principle result in different dose-response relations at high doses compared with the LQ approach in which repair rates are dose independent.

In fact, there is not, as yet, strong evidence that SR mechanisms are important at the doses and dose rates of relevance to radiotherapy.[44] However, because SR models appear, prima facie, to be mechanistically different from binary misrepair models, there is the possibility that they could make significantly different predictions of fractionation/protraction effects, casting doubt on the validity of LQ-based isoeffect dose calculations. In fact, the formalisms describing most SR models also lead, in an appropriate approximation, to the same time-dose relations as does the LQ formalism.[32] This comes about because these SR formalisms reduce to the specific form of the generalized Lea-Catcheside time factor, G, which describes protraction effects in the LQ approach.

Figure 5 gives numeric estimates comparing the predictions of a typical SR formalism,[39,45] with the corresponding LQ predictions at doses of relevance to radiotherapy.[32] Specifically, in a comparison of any 2 practical fractionated external-beam radiotherapeutic regimens, the predicted isoeffect doses are very similar using either the LQ or the SR formalism. For example, for a single-fraction dose of 5 Gy, using equivalent parameters, the LQ and the SR model would give cell-survival predictions that differed by only about 0.18%; thus, for a ten-fraction 5 Gy per fraction prostate hypofractionation protocol, the LQ and the SR model would differ in cell-survival predictions by only about 1.8%.

Although Figure 5 refers to the practical equivalence of a particular SR formalism to LQ, other SR models also show this equivalence. For example, for the SR model described by

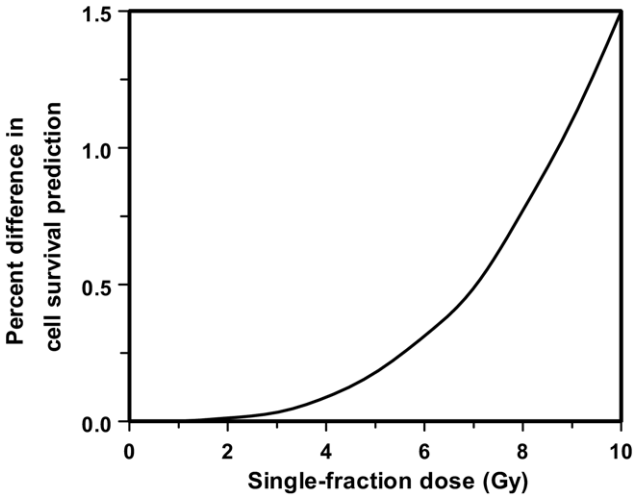

Figure 5 For a single acute dose fraction shown is the percent relative difference [$100(S_{SR}$-$S_{LQ})/S_{SR}$] between survival calculated exactly using the SR model and survival calculated using the corresponding LQ approximation. Calculations reported in Brenner et al[32] based on the parameter set from Kiefer and Löbrich.[45]

Sontag,[43] which is conceptually similar although described by a slightly different formalism, a corresponding theorem on equivalence to LQ can be proven.[32] More generally, it can be shown that formalisms describing a very broad class of radiobiological reaction rate models, whether based on binary misrepair or SR repair, all lead to the same generalized Lea-Catcheside time factor, G, for dose protraction.[32]

Conclusions

Typing "linear-quadratic" and "radiotherapy" into PubMed results in over 600 hits, so LQ is very widely used. Even with this extensive use, there is to date no evidence that the use of LQ has resulted in significant underdosing or overdosing for alternate fractionation schemes.

It is important to distinguish here between the validity of the LQ model and the appropriate parameters to use in the LQ approach; these are different issues. For example, the suggestion that the α/β ratio for prostate cancer is anomalously low[46,47] has resulted in several large randomized trials, all designed using LQ, comparing conventional fractionation to hypofractionation.[48] Such trials are explicitly based on mechanistic considerations quantified with the LQ model and would today be inconceivable without the conceptual framework of an established mechanistic model.

What is the dose per fraction range for which the LQ model should be used? It has been argued here, based both on experimental and theoretical considerations, that LQ is a reliable mechanistically plausible model for designing protocols in the dose per fraction range from 2 to 10 Gy. Above 10 Gy, the model would be expected to become progressively less accurate but, based on animal data, still acceptable for the design of clinical trials based on doses per fraction of 15 to 18 Gy.

That the LQ model is useful over such a wide dose range is related to the observation that almost all mechanistic models of cell killing predict essentially the same dependencies for fractionation as does LQ, so the use of LQ is not as model dependent as one might expect. Of course, the basic LQ model does not tell the whole story. Fractionation/protraction effects are controlled[49] by the 4 R's (repair, redistribution, reoxygenation, and repopulation). At the cost of extra parameters, the remaining 3 R's can be modeled using LQ,[50,51] although it is clear that fractionation effects are dominated by repair.

In summary, LQ has the following useful properties for predicting isoeffect doses:

1. It is a mechanistic, biologically based model.
2. It has sufficiently few parameters to be practical.
3. Most other mechanistic models of cell killing predict the same fractionation dependencies as does LQ.
4. It has well-documented predictive properties for fractionation/dose-rate effects in the laboratory.
5. It is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction.
6. To date, there is no evidence of problems when LQ has been applied in the clinic.

Alfred North Whitehead commented that "There is no more common error than to assume that, because prolonged and accurate mathematical calculations have been made, the application of the result to some fact of nature is absolutely certain."[52] This is certainly true for the LQ model and all other mechanistically based models used to design alternate fractionation protocols. Adding clinical judgment to the results of radiobiological modeling is a must.

References

1. Fowler JF: The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62:679-694, 1989
2. Thames HD, Hendry JH: Fractionation in Radiotherapy. New York, Taylor & Francis, 1987
3. Dale RG: The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol 58:515-528, 1985
4. Lea DE: Actions of Radiation on Living Cells. Cambridge, University Press, 1946
5. Sachs RK, Hahnfeld P, Brenner DJ: The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. Int J Radiat Biol 72:351-374, 1997
6. Ellis F: Is NSD-TDF useful to radiotherapy? Int J Radiat Oncol Biol Phys 11:1685-1697, 1985
7. Turesson I, Notter G: Skin reaction as a biological parameter for prospective studies of different dose schedules with the CRE formula. Bull Cancer 63:11-26, 1976
8. Bates TD, Peters LJ: Dangers of the clinical use of the NSD formula for small fraction numbers. Br J Radiol 48:773, 1975
9. Peters LJ, Withers HR: Morbidity from large dose fractions in radiotherapy. Br J Radiol 53:170-171, 1980
10. Gerweck LE, Zaidi ST, Zietman A: Multivariate determinants of radiocurability. I: Prediction of single fraction tumor control doses. Int J Radiat Oncol Biol Phys 29:57-66, 1994
11. Brown M, Bristow R, Glazer P, et al: Comment on "tumor response to radiotherapy regulated by endothelial cell apoptosis" (II). Science 302: 1894, 2003
12. Preston RJ: Mechanisms of induction of specific chromosomal alterations. Basic Life Sci 53:329-336, 1990

13. Wlodek D, Hittelman WN: The relationship of DNA and chromosome damage to survival of synchronized X-irradiated L5178Y cells. II. Repair Radiat Res 115:566-575, 1988
14. Savage JR: A brief survey of aberration origin theories. Mutat Res 404: 139-147, 1998
15. Lea DE, Catcheside DG: The mechanism of the induction by radiation of chromosome aberrations in tradescantia. J Genet 44:216-245, 1942
16. Kellerer AM, Rossi HH: The theory of dual radiation action. Curr Top Radiat Res 8:85-158, 1972
17. Thames HD: An 'incomplete-repair' model for survival after fractionated and continuous irradiations. Int J Radiat Biol 47:319-339, 1985
18. Brenner DJ, Huang Y, Hall EJ: Fractionated high dose-rate versus low dose-rate regimens for intracavitary brachytherapy of the cervix: Equivalent regimens for combined brachytherapy and external irradiation. Int J Radiat Oncol Biol Phys 21:1415-1423, 1991
19. Fowler JF, Ritter MA, Chappell RJ, et al: What hypofractionated protocols should be tested for prostate cancer? Int J Radiat Oncol Biol Phys 56:1093-1104, 2003
20. Prevost JB, Voet P, Hoogeman M, et al: Four-dimensional stereotactic radiotherapy for early stage non-small cell lung cancer: A comparative planning study. Technol Cancer Res Treat 7:27-34, 2008
21. Brenner DJ, Martel MK, Hall EJ: Fractionated regimens for stereotactic radiotherapy of recurrent tumors in the brain. Int J Radiat Oncol Biol Phys 21:819-824, 1991
22. Bartkowiak D, Hogner S, Nothdurft W, et al: Cell cycle and growth response of CHO cells to X-irradiation: Threshold-free repair at low doses. Int J Radiat Oncol Biol Phys 50:221-227, 2001
23. Garcia LM, Leblanc J, Wilkins D, et al: Fitting the linear-quadratic model to detailed data sets for different dose ranges. Phys Med Biol 51:2813-2823, 2006
24. Barendsen GW: Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys 8:1981-1997, 1982
25. van der Kogel AJ: Chronic effects of neutrons and charged particles on spinal cord, lung, and rectum. Radiat Res Suppl 8:S208-S216, 1985
26. Douglas BG, Fowler JF: The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. Radiat Res 66: 401-426, 1976
27. Peck JW, Gibbs FA: Mechanical assay of consequential and primary late radiation effects in murine small intestine: Alpha/beta analysis. Radiat Res 138:272-281, 1994
28. Taylor JM, Kim DK: The poor statistical properties of the Fe-plot. Int J Radiat Biol 56:161-167, 1989
29. de Boer RW: The use of the D versus dD plot to estimate the alpha/beta ratio from iso-effect radiation damage data. Radiother Oncol 11:361-367, 1988
30. Tucker SL: Tests for the fit of the linear-quadratic model to radiation isoeffect data. Int J Radiat Oncol Biol Phys 10:1933-1939, 1984
31. Ling CC, Chen CH, Fuks Z: An equation for the dose response of radiation-induced apoptosis: Possible incorporation with the LQ model. Radiother Oncol 33:17-22, 1994
32. Brenner DJ, Hlatky LR, Hahnfeldt PJ, et al: The linear-quadratic model and most other common radiobiological models result in similar predictions of time-dose relationships. Radiat Res 150:83-91, 1998
33. Curtis SB: Lethal and potentially lethal lesions induced by radiation—A unified repair model. Radiat Res 106:252-270, 1986
34. Hawkins RB: A microdosimetric-kinetic model of cell death from exposure to ionizing radiation of any LET, with experimental and clinical applications. Int J Radiat Biol 69:739-755, 1996
35. Obaturov GM, Moiseenko VV, Filimonov AS: Model of mammalian cell reproductive death. I. Basic assumptions and general equations Radiat Environ Biophys 32:285-294, 1993
36. Tobias CA: The repair-misrepair model in radiobiology: Comparison to other models. Radiat Res Suppl 8:S77-S95, 1985
37. Zaider M: There is no mechanistic basis for the use of the linear-quadratic expression in cellular survival analysis. Med Phys 25:791-792, 1998
38. Sachs RK, Brenner DJ: The mechanistic basis of the linear-quadratic formalism. Med Phys 25:2071-2073, 1998
39. Kiefer J: A repair fixation model, in Kiefer J (ed): Quantitative Mathematical Models in Radiation Biology. New York, Springer-Verlag, 1988
40. Haynes RH: The interpretation of microbial inactivation and recovery phenomena. Radiat Res Suppl 6:1-29, 1966
41. Laurie J, Orr JS, Foster CJ: Repair processes and cell survival. Br J Radiol 45:362-368, 1972
42. Reddy NM, Mayer PJ, Lange CS: The saturated repair kinetics of Chinese hamster V79 cells suggests a damage accumulation–interaction model of cell killing. Radiat Res 121:304-311, 1990
43. Sontag W: A cell survival model with saturable repair after irradiation. Radiat Environ Biophys 26:63-79, 1987
44. Ward JF, Limoli CL, Calabro-Jones PM, et al: An examination of the repair saturation hypothesis for describing shouldered survival curves. Radiat Res 127:90-96, 1991
45. Kiefer J, Lobrich M: The repair fixation model, general aspects and the influence of radiation quality, in Chadwick KH, Moschini G, Varma M (eds): Biophysical Modelling of Radiation Effects. New York, Adam Hilger Press, 1992, pp 211-218
46. Brenner DJ, Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 43:1095-1101, 1999
47. Duchesne GM, Peters LJ: What is the α/β ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 44:747-748, 1999
48. Miles EF, Lee WR: Hypofractionation for prostate cancer: A critical review. Semin Radiat Oncol 18:41-47, 2008
49. Haustermans K, Withers HR: The biological basis of fractionation. Rays 29:231-236, 2004
50. Brenner DJ, Hlatky LR, Hahnfeldt PJ, et al: A convenient extension of the linear-quadratic model to include redistribution and reoxygenation. Int J Radiat Oncol Biol Phys 32:379-390, 1995
51. Travis EL, Tucker SL: Isoeffect models and fractionated radiation therapy. Int J Radiat Oncol Biol Phys 13:283-287, 1987
52. Whitehead AN: Introduction to mathematics. New York, H. Holt, 1911, p 27