A new isoeffect curve for change in dose per fraction

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Summary

A method is proposed for using survival curve parameters for calculating the change in total dose necessary to achieve an equal response in a tissue when the dose per fraction is varied. The method uses the ratio $\alpha/\beta$ of the coefficients of the linear quadratic survival formula and accounts only for the effect of repair of cellular injury. Absolute values for $\alpha$ and $\beta$ are not required. The isoeffect curves vary for different tissues. A dose adjustment to account for differences in the regeneration of surviving cells that might result from changing a treatment regimen must be made separately and will also vary from tissue to tissue. Examples of the use of the curves are given. At present, the curves, particularly those for late effects, are uncertain and caution should be observed in using them until they are defined more accurately with additional data.

Introduction

No single isoeffect curve can describe the dose-fractionation response of all tissues. Processes that influence the response to multifraction irradiation (repair of sublethal and potentially lethal damage, regeneration of surviving cells, including recruitment into cycle of non-cycling cells, redistribution through the division cycle and reoxygenation) vary between tissues and tumors, and with time for the same tissue or tumor. Therefore, it is unreasonable to describe fractionation responses with parameters that are universal and constant. The purpose of this paper is to suggest a simple method by which the radiotherapist can allow for the major determinant of multifraction response, i.e. repair capacity, when he wishes to change the size of dose per fraction without significantly altering the duration of treatment.

A new isoeffect formula

Clinical and laboratory data indicate significant differences in the changes in severity of response in different tissues when the size of dose per fraction in a multifractionated regimen is changed [10, 21, 22]. In particular, it has been noted that when larger than conventional dose fractions are given, the severity of sequelae in late-responding tissues is increased relative to those in acutely responding tissues. When regeneration of surviving cells can be disregarded, the major factor determining this differential between acutely and slowly responding tis-
sues is variation in the capacity for intracellular repair of radiation injury [1, 10, 21, 22]. Significant regeneration could alter this differential by means of cell replenishment, although other factors, such as cell-cycle redistribution [20, 23] or the rate of expression of injury [5, 16] could also be implicated.

Empirical isoeffect concepts such as the NSD, CRF and TDF were based on changes in the responses of skin and epithelial tumors with altered dose fractionation. More recently, isoeffect formulations [e.g. 1, 2, 10, 22] have been derived from dose-survival models such as the linear-quadratic survival relationship

\[ S = (e^{-\xi d + \xi d^2})^N \]

since it is not unreasonable to assume that given levels of tissue damage correspond to specific surviving fractions of target cells. In this formula, \( S \) is surviving fraction, \( d \) is the size of dose per fraction, \( N \) is the number of dose fractions, and \( \xi \) and \( \beta \) are constants. While this model has traditionally been applied to describe clonogenic cell survival, in the present instance it is intended to reflect also decrement in tissue function, occurring through loss of putative target cells. Therefore, \( \alpha \) would represent "single-hit" killing, and \( \beta \) would encompass any repair process in the tissue.

Cell survival determined from in vivo colony assays is described equally well by survival curves determined using the linear-quadratic model or the more traditional two-component model [8, 9, 12]. However, it appears that the linear-quadratic model is better suited to the description of tissue responses [6]. Therefore, in the following it will be assumed that the linear-quadratic survival equation adequately describes tissue responses to fractionated doses, and further, that the fit is adequate over a fairly wide range of doses per fraction (e.g. 0–10 Gy). Given these, and the usual assumptions governing the validity of applying cell-survival models to the description of tissue responses [e.g. 1, 2, 6, 7, 10, 21, 22], isoeffect curves will be constructed that can be extrapolated to doses of clinical concern (e.g. 1–4 Gy) using experimental data derived from experiments in which doses per fraction of 3–10 Gy are more commonly employed.

The starting point is the observation that the ratio \( \beta/\alpha \) of parameters of the linear-quadratic survival model provides a simple measure of tissue sensitivity to changes in size of dose per fraction [10]: late-responding normal tissues are characterized by larger values of \( \beta/\alpha \) than are those that respond acutely. This ratio can be determined for different tissues from their response to multifractionated radiation, using either isoeffect doses for functional endpoints [2] or from survival data obtained from in vivo colony assays [8, 9, 11, 12].

While the ratio \( \beta/\alpha \) is a direct measure of tissue sensitivity to changes in dose fractionation (and enjoys other advantages, such as finiteness for all qualities of radiation or stages of the cell cycle, etc.), for present purposes, it is convenient to work in terms of its reciprocal, \( \alpha/\beta \), to make computations easier. Also, the relationship of \( \alpha/\beta \) to fractionation sensitivity can be thought of in terms of the “flexure dose” [11], the dose per fraction whose further reduction results in no detectable increase in tissue sparing. The flexure dose can be shown to be a multiple of the ratio \( \alpha/\beta \) [11]. Therefore, characterization of sensitivity to dose fractionation in terms of \( \alpha/\beta \) may be thought of as a specification of flexure doses for various tissues. Flexure doses have been shown to be small for late-reacting tissues, and large for acutely reacting tissues [11].

The most commonly used dose per fraction in radiotherapy is 2 Gy. Radiation oncologists need to know, for a given clinical situation, how to modify the total dose “tolerated” as 2 Gy fractions when the size of dose per fraction is changed. If it is assumed that the linear-quadratic model is appropriate for cell survival, or tissue response, the ratios of total doses \( D/D_{\text{ref}} \) (where \( D_{\text{ref}} \) is the isoeffective total dose in the standard regimen and \( D \) is the total dose that is to be determined) can be calculated as a function of dose per fraction from the formula

\[
\frac{D}{D_{\text{ref}}} = \frac{\alpha/\beta + d_{\text{ref}}}{\alpha/\beta + d}
\]

where \( d_{\text{ref}} \) is the dose per fraction in the standard regimen (usually 2 Gy), \( d \) is the new dose per frac-
Fig. 1. Theoretical isoeffect curves relating total doses for an isoeffect to changes in dose per fraction for different values of \( \alpha/\beta \). Total doses for equal effects are expressed as a ratio or percentage of the total dose “tolerable” in 2 Gy fractions. It is assumed that the only variable is change in dose per fraction and that repair of sublethal and potentially lethal damage is complete between dose fractions. Phenomena that would lead to unequal effects per fraction (e.g. regeneration of surviving cells, reoxygenation, variable division cycle redistribution) are not accounted for by these curves.

Figure 1 shows hypothetical curves relating the ratio of total doses for an isoeffect for departures from a 2 Gy per fraction regimen for different values of \( \alpha/\beta \). Features of the curves in Fig. 1 are:

(a) They are constructed assuming an equal effect per fraction which requires that repair of sublethal damage between fractions be complete, and that either there be no contribution to the responses from other factors, or that a dynamic heterogeneity, e.g. of cell cycle redistribution, ensures equality per fraction.

(b) The curves do not adjust for differences in regeneration during treatment when a change is made from a 2 Gy per fraction regimen. In tissues where a significant regenerative response may be expected, it is assumed that it will be the same in the modified regimen as in the conventional 2 Gy per fraction regimen. If not, an additional adjustment to the total dose must be made initially.

(c) The relationship considers only size of dose per fraction and not the number of fractions, making it independent of the different total doses necessary for isoeffects in different tissues. This is one characteristic that distinguishes the present approach from NSD, CRE or TDF formulations.

(d) The smaller the \( \alpha/\beta \) ratio, the greater the sensitivity to dose fractionation of a tissue and hence the greater the change in ratio of total isoeffective doses with change in size of dose per fraction. For example, to produce the same effect as 60 Gy in 2 Gy fractions using 3 Gy fractions would require about 55.5 \((.925 \times 60)\) Gy in a tissue characterized by an \( \alpha/\beta \) ratio of 10 Gy compared with about 47.4 \((.79 \times 60)\) Gy in one characterized by an \( \alpha/\beta \) ratio of 1.7 Gy.

In Fig. 2, some curves are presented in which \( \alpha/\beta \) ratios determined for a variety of tissues in experimental animals \([2-4, 8, 9, 12-15, 17-19]\) were used to construct isoeffect curves similar to those presented in Fig. 1. The data were selected because it was considered that they were not influenced by incomplete repair of sublethal damage, regeneration, or reoxygenation. However, a contribution to the multifraction responses from cell cycle redistribution cannot be excluded, especially in acutely responding tissues (dashed curves). Note that:
(a) All the acutely responding tissues, including micrometastases of a fibrosarcoma, are characterized by a similar $\alpha/\beta$ ratio and this ratio is greater than that characteristic of the more slowly responding tissues.

(b) Isoeffect curves for the slowly responding tissues in experimental animals (lung, cervical cord) corroborate the clinical observation that greater changes in doses are necessary for an isoeffect if the dose per fraction is varied than is the case for acutely responding tissues.

(c) Few data exist in the range most important to clinical radiation oncologists. Confident extrapolation of the isoeffect curves to doses of 1–3 Gy requires that further data be obtained at those doses per fraction and/or that the linear quadratic model be shown to be a good fit to the responses of a spectrum of tissues over a wide range of doses.

(d) The dissociation between the isoeffect curves for slowly and acutely responding tissues, including one tumor, suggests that if most tumors show an acute response to irradiation, and late effects are dose-limiting, a therapeutic gain can be achieved from the use of dose fractions less than 2 Gy, provided, of course, that other factors in the relative multifraction responses of the tumor and normal tissues are equal [7].

**Examples of clinical application using Fig. 2**

(1) If, in the treatment of head and neck cancer, a radiotherapist normally reduces his fields off the spinal cord at a dose of 46 Gy in daily fractions of 2 Gy, at what dose should the field reduction be made to preserve the same margin of safety for the spinal cord if circumstances require a modified treatment using fractional doses of 4.2 Gy given twice weekly?

*Solution.* Enter Fig. 2 at 4.2 Gy on the abscissa and locate the corresponding point on the curve labeled “cervical cord”. Note the value of the ordinate at this point (0.65) and multiply by 46 Gy to give the answer of 29.9 Gy. Round this to the next lowest even multiple of 4.2 Gy to be conservative, i.e. make the field reduction after 7 fractions totaling 29.4 Gy.

**Comments.** Because little or no regeneration would be expected in the spinal cord over the proposed duration of treatment, no adjustment of total dose for this change of time from 4.5 to 3.5 weeks is necessary. Note that using the TDF tables, the corresponding isoeffect dose (TDF = 76) would be given by 8 fractions of 4.2 Gy delivered twice weekly. This illustrates the greater risk of overdosage for late normal tissue injury when the NSD formulation is used.

(2) In the external beam treatment of gynecologic malignancy, what dose in 3 Gy fractions given over 4 weeks would be expected to produce a comparable incidence of diarrhea as 40 Gy in 2 Gy fractions over 4 weeks?

*Solution.* Entering Fig. 2 at 3 Gy on the abscissa, locate the corresponding point on the “colon” curve, read off the value on the ordinate at this point (0.92) and multiply by 40 Gy to give the answer of 36.8 Gy. Round down to 12 fractions of 3 Gy given over 4 weeks.

**Comments.** For acute normal tissue endpoints, the overall duration of treatment must be kept constant in order to use the figure, since no allowance for different amounts of regeneration is made. If the overall treatment duration were to be less than 4 weeks, a reduction in total dose to account for decreased mucosal regeneration should be made before applying a correction for altered dose per fraction.

**Conclusions**

The relative values of $\alpha/\beta$ ratios for late-responding normal tissues and a murine tumor, as reflected in the curves in Fig. 2, suggest that a therapeutic disadvantage would result from using large dose fractions, and that conversely, an advantage may accrue from reducing dose per fraction below 2 Gy [7, 20] provided variables other than dose per fraction are accounted for. This is illustrated by the steeper isoeffect curves for late effects [10, 21, 22] which may be calculated as described in this paper. The method of calculating isoeffective doses is sub-
ject to error and, as already indicated, more data are needed to refine existing estimates of \( x/\beta \) for different tissues and volumes of the same tissue. The experimental data at present, especially those for late effects at small doses per fraction, are simply too uncertain to permit an accurate prediction of the extent to which hyperfractionation would increase the tolerance of critical normal tissues such as the spinal cord, and we would urge caution in using this method to predict isoeffect doses for fractional doses below those for which clinical or experimental data exist.

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References