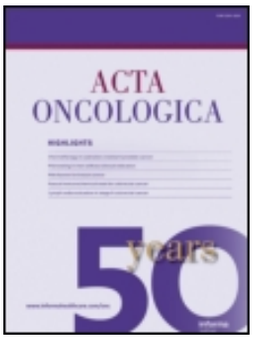

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ORIGINAL ARTICLE

Steepness of the radiation dose-response curve for dose-per-fraction escalation keeping the number of fractions fixed

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Abstract
Clinically, there is growing interest in strategies for intensifying radiation therapy by escalating the dose per fraction. This paper considers the steepness of the dose-response curve in this case. The steepness of a radiation dose-response curve is most conveniently quantified by the normalized dose-response gradient, γ. Under the assumption of a linear-quadratic dose-effect model, a simple analytical relationship is derived between the γ-value for a dose-response curve generated by varying the total dose while keeping the number of fractions constant, i.e. escalating the dose per fraction, and the γ-value for a dose-response curve generated by varying the total dose while keeping the dose per fraction constant. This formulation is compared with clinical dose-response data from the literature and shown to be in good agreement with the observations. Some implications of this formulation for non-uniform dose distributions delivered using 3D conformal radiotherapy or intensity modulated radiotherapy (IMRT) are briefly discussed.

Dose-response relationships are of fundamental importance in practical and theoretical radiotherapy, and in a variety of applications it turns out that it is the steepness of the dose-response curve, rather than its position, that is of prime interest [1]. A convenient measure of the steepness of the dose-response curve is the normalized dose-response gradient, γ [2,3]. Clinical dose-response curves are estimated from observations of clinical outcome at two or more dose levels, traditionally often keeping the dose per fraction, *d*, constant as dosage is escalated. We use the notation γ_d for the normalized dose-response gradient in this situation. For the standard formulations of the dose-response curve it is easily shown that γ_d at the point of maximum steepness of the dose-response curve is independent of the size of dose per fraction, a property making this a convenient parameter for summarizing the results of a dose-response study.

Recently, there has been a growing interest in dose-per-fraction escalation. This has been stimulated by attempts to accelerate radiotherapy without going to multiple fractions per day [4], to reduce workload and improve patient convenience [5], or as a result of new radiobiological data suggesting that the fractionation sensitivity of some human tumors may be higher than conventionally thought [6–10]. Also, the ability of intensity modulated radiation therapy (IMRT) to deliver a highly non-uniform dose to the tumor has stimulated interest in strategies whereby the dose to a subvolume of the tumor is boosted by increasing the local dose per fraction to that volume [11–13]. It has long been appreciated that the dose-response relationship is steeper in these situations. If γ_N denotes the γ-value generated with a fixed number of fractions, *N*, it follows from the assumed validity of the linear-quadratic (LQ) model that $\gamma_N > \gamma_d$. This is a direct consequence of what Withers [14] called 'double trouble': an increase in dose is accompanied by a change in dose per fraction when the number of fractions is kept constant. Due to the linear-quadratic dose-effect relationship this leads to an increase in the biological effectiveness per Gy absorbed dose.

Several authors, including the present one, have considered the relationship between γ_N and γ_d and have often arrived at fairly complicated expressions for γ_N using the LQ-model [2,3,15–17]. Most of these relationships have involved both the dose of interest and in case of the Poisson dose-response

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model the absolute value of the β-parameter of the LQ-model or, in case of the logistic model, the regression coefficient for the dose-squared term in the dose-response model. In the present communication, a much simpler and more convenient general relationship is derived, and its implications are briefly discussed.

Relationship between γ_N and γ_d

The normalized dose-response gradient for a dose-response curve, P(D), is defined as

$$\gamma = D \cdot \frac{dP}{dD} \tag{1}$$

Note, that γ is a function of dose (or response level) but that this is normally suppressed in the notation for convenience. We assume in the following that the linear-quadratic model is valid for converting a dose delivered in N fractions with a constant dose per fraction, x, into the biologically equivalent dose when delivered with a reference dose per fraction, d_r. We introduce the notation

$$f(x) = N \cdot x \cdot \frac{{}^{\alpha}/_{\beta} + x}{{}^{\alpha}/_{\beta} + d_r}. \tag{2}$$

This is easily recognized as "Withers' formula" [18]: for a given dose per fraction, x, f(x) is the biologically equivalent dose delivered in dose per fraction, d_r. The response after a dose D delivered in N fractions is simply calculated by inserting the biologically equivalent dose delivered with the constant dose per fraction d_r into the dose-response function P(D). If we define $x_0 = D/N$ we can apply the chain rule from elementary calculus in order to derive the following expression for γ_N:

$$\begin{aligned} \gamma_N(f(x_0)) &= f(x_0) \cdot P'(f(x))|_{x=x_0} \\ &= f(x_0) \cdot P'(f(x_0)) \cdot f'(x)|_{x=x_0} \\ &= \gamma_d(f(x_0)) \cdot \frac{{}^{\alpha}/_{\beta} + 2 \cdot x_0}{{}^{\alpha}/_{\beta} + d_r} \end{aligned} \tag{3}$$

In practice, we are often interested in the relationship between γ_N and γ_d at the specific dose per fraction x_0. To this end, we choose the reference dose so that $x_0 = d_r$, then Equation 3 becomes

$$\gamma_N = \gamma_d \cdot \frac{{}^{\alpha}/_{\beta} + 2 \cdot d_r}{{}^{\alpha}/_{\beta} + d_r} \tag{4}$$

Note, that no specific mathematical form of the dose-response function is assumed (mathematically, P(D) just has to be differentiable with a continuous first derivative). Note, also that Equation 4 is locally valid around the dose $D_r = N \cdot d_r$ but that there are no restrictions on the choice of this reference dose, d_r As D varies d_r will vary because of N being constant.

A few observations follow immediately from Equation 4. As both α/β and d_r are positive numbers, γ_N is always larger than γ_d irrespective of the dose per fraction and the fractionation sensitivity of the tissue. Two asymptotic properties are also clear:

$$\lim_{d_r \to \infty} \gamma_N = 2 \cdot \gamma_d \tag{5}$$

and

$$\lim_{d_r \to 0} \gamma_N = \gamma_d \tag{6}$$

Equation 6 is intuitively clear: tissues with $\alpha/\beta >> d_r$ will exhibit low fractionation sensitivity, and it is the fractionation effect that causes the double trouble phenomenon.

Finally, it follows immediately from Equation 4 that if we change the dose per fraction from d_1 to d_2 then the steepness of the dose response curve for a fixed N will change as follows:

$$(\gamma_N)_2 = (\gamma_N)_1 \cdot \frac{{}^{\alpha}/_{\beta} + 2 \cdot d_2}{{}^{\alpha}/_{\beta} + d_2} \cdot \frac{{}^{\alpha}/_{\beta} + d_1}{{}^{\alpha}/_{\beta} + 2 \cdot d_1} \tag{7}$$

Application to a clinical data set

A unique opportunity for testing the relationship (Equation 4) between γ_d and γ_N based on empirical clinical data is provided by Ingela Turesson's clinical study [19] of dose-response relationships for 'partially-confluent' telangiectasia. Other studies have estimated α/β for this endpoint at 2.7 Gy [20,21], and analysis of a large set of dose-response curves generated using a fixed dose per fraction showed that $\gamma_d \approx 4$ on the steep part of the curve [19]. Turesson reports γ-values for two clinical dose-response curves generated with a fixed number of fractions: for $N = 4$, d_r is around 7.2 Gy at the 50% response level. Inserting this value into Equation 4 yields an estimated $\gamma_4 = 6.9$, in good agreement with the empirical γ-value of 6.4; for $N = 1$, d_r is 15.6 Gy at the 50% response level and the estimated γ_1 is 7.4 in very good agreement with the observed γ-value of 7.3

Discussion and conclusion

A relationship that is formally similar to the one derived in Equation 4 above has previously been suggested to hold up as an approximate relationship at the steepest part of the dose-response curve in the special case of a Poisson dose-response model [15]. As shown here, this formula is valid irrespective of the details of the dose-response curve, at all response levels and without any approximation. This is of

potential interest for several current developments in radiation oncology.

Doses per fraction exceeding the conventional 2 Gy are returning to clinical radiotherapy. This is partly based on the emergence of new radiobiological parameter estimates and partly on health economics grounds [22]. Also, the reduction in volume of critical normal-tissues receiving a high dose from 3D conformal or intensity modulated radiotherapy may allow delivering fewer, larger fractions than the standard 2 Gy fractions without compromising the therapeutic ratio [22].

Precision requirements for hypo-fractionation are stricter than for conventionally fractionated therapy. Intuitively, it is clear that if a larger proportion of the total biological effect is delivered in each fraction, then the geometrical and dosimetric precision should be relatively higher to maintain a constant patient-to-patient variability in treatment outcome. The resulting variation in mean dose springing from the fraction-to-fraction (random) variability is inversely proportional to the square-root of the number of fractions. In other words, if we reduce the number of fractions by a factor of 4, we should reduce the random fraction-by-fraction error by a factor of two, in order to have the same overall uncertainty from the random component.

For hypo-fractionation, the patient-level dosimetric precision required to retain the same spread of the distribution of clinical outcome, is inversely proportional to the steepness of the dose-response curve, or more precisely to $\gamma_{N,}$ as the prescribed number of fractions is fixed in a cohort of patients receiving a specific schedule. Equation 4 implies that with increasing dose per fraction that is increasing d_r, the patient-level precision requirement will also increase. It is remarkable, though, by application of Equation 7 that this relative change in required precision is relatively modest. For a late-responding normal tissue with high fractionation sensitivity, say, with $\alpha/\beta = 2$ Gy, the relative change in γ_N when increasing dose per fraction from 2 Gy to 5 Gy is just 14% The limiting value of this relative change in required precision at very high dose per fraction is 33%, which again is a relatively modest increase.

Another application of γ_N is in the consideration of hot spots in normal-tissue dose distributions [14]. There is one important caveat: In this situation the volume effect in the tissue or organ of interest will have to be taken into account. Direct application of γ_N to a change in hot spot dose will in most situations over-estimate the resulting change in normal-tissue complication probability. This is perhaps even more of an issue in current radiotherapy where 3D conformal radiotherapy and IMRT often give rise to highly non-uniform dose distributions in critical normal structures. There are two different approaches to tackle this situation. One is following Lind et al. [23] who generalized the standard γ concept to an arbitrary non-uniform 3D distribution. The other more pragmatic approach is based on derivation of a summary dose from the dose-volume histogram. The standard example is the Lyman model, see for example Tucker et al. [24], where it is easily shown [25] that the normalized dose-response gradient $\gamma = \frac{1}{m \cdot \sqrt{2\pi}}$. Here, m is the (inverse) steepness parameter in the standard formulation of this model. In addition the model includes a position parameter as well as other parameters used to define a dosimetric summary measure of the dose-volume histogram. This could for example be the generalized equivalent uniform dose, gEUD. The γ-value in this situation applies to, and is empirically derived from, the probit dose response curve as a function of the gEUD.

In conclusion, we have derived a simple relationship for the steepness of the dose-response curve delivered with a fixed number of fractions. The formula derived is shown to be consistent with the only precise quantitative estimates from clinical data. Finally, we have discussed some implications of this relationship for theoretical considerations of outcome after altered fractionation in radiotherapy.

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