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Quantifying the position and steepness of radiation dose–response curves

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Abstract. Radiation dose–response curves are of fundamental importance both in practical radiotherapy and as the basis of more theoretical considerations concerning the potential benefit to be gained from modified dose–fractionation schedules or of the effects of dosimetric and biological variability. The steepness of the dose–response curve is a key parameter and quantitative measures of steepness derived from clinical data are strongly needed. Unfortunately, there are many ambiguities associated with quantifying the steepness of radiation dose–response curves and these are identified and discussed in the present paper. The following problems are reviewed. (1) In the literature, various descriptors of 'steepness' are reported. We focus on the normalized dose–response gradient, γ, and the dose–response slope, θ. The mathematical properties and the relationship between these are discussed. (2) Steepness estimates depend on the mathematical model used to describe the dose–response relationship. Three standard formulations are considered: the Poisson, the logistic and the probit dose–response model. The magnitude of the model dependence is influenced by the range of the empirical dose–response data available, and is most pronounced for data concentrated around very low or very high response levels. (3) Reparametrizations of the standard models in terms of position and steepness are given, and it is pointed out that some previously published formulas are only approximations. (4) The method of analysis can influence the steepness estimate. An analysis of a specific data set shows that the use of the least-squares method rather than the preferred maximum likelihood method may influence both the steepness estimate and its confidence interval. (5) Dose–response data generated with a fixed number of fractions rather than a fixed dose per fraction will produce steeper dose–response curves. The approximation involved in describing such a set of dose–response data by a position and a single steepness parameter is discussed. (6) The importance of specifying the statistical uncertainty of the steepness estimate is stressed. All of these problems are illustrated by a practical example, in which dose–response data from the literature are re-analysed.

1. Introduction

Dose–response relationships for tumour control and the incidence of specific normal-tissue effects after radiotherapy are of obvious importance in optimizing radiotherapy prescriptions (Holthusen 1936, Fletcher 1973, Morrison 1975, Perez and Brady 1992). Also, they are the basis of more theoretical considerations, e.g. of the influence of uncertainty in treatment planning and delivery (Herring 1975, Svensson *et al.* 1975, Goitein 1979, Brahme 1984) or in the design of clinical trials with a radiobiological rationale (Bentzen 1994).

Empirically, dose–incidence data for a specific radiation effect, an endpoint, follow a sigmoid, or s-shape, curve. Several mathematical functions have been used to model the relationship between radiation dose and tumour control probability or normal-tissue complication probability. Although the particulars of the published analyses vary, the most frequently used models have one of three mathematical forms: the Poisson, the logistic or the probit model. For endpoints requiring prolonged follow-up of the patient, like local control or late normal-tissue reactions, these models may be embedded in a so-called mixture model (Bentzen *et al.* 1989), in which the time to occurrence of the endpoint is also taken into account. There, the dose–response model may be interpreted as describing the ultimate incidence, i.e. the incidence at long follow-up, of the endpoint in question. A fourth type of dose–response model arises from the Cox Proportional Hazards Model, which is also applied to analyse time-to-occurrence data (Taylor *et al.* 1987), but this will not be considered here.

The position of the dose–response curve is most often quantified by the dose required to obtain a specified level of response, say 37% (the D_{37}) or 50% (the D_{50}). Various measures have been used to quantify the steepness of the dose–response curve including the effective D_0 (Withers and Peters 1980) or apparent D_0 (Bentzen and Thames 1991), the relative dose increment required to increase response from 20 to 80% (Goitein 1979), from 40 to 60% (Williams *et al.* 1984), from 25 to 75%, or from 50 to 75% (Mijnheer *et al.* 1987), the probit width of the dose–response curve (Moore *et al.* 1983), the slope of the line tangent to the dose–response curve (Hendry and Moore 1985), or the dose required to increase response from 37 to 50% (Thames *et al.* 1980) or

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from 50 to 90% (Trott *et al.* 1984). These measures are not always readily convertible from one to the other. Therefore, this variety in published measures of steepness has often made it difficult to compare the results of different studies.

In 1984, Brahme introduced a quantity called the normalized dose–response gradient, denoted by γ, for describing the steepness of the dose–response curve. γ represents the increase in response, in percentage points, for a 1% increase in dose, and this has become the preferred descriptor of steepness in recent years (Suit and Walker 1989, Thames *et al.* 1991, Suit *et al.* 1992, Bentzen 1994, Munzenrider and Crowell 1994, Okunieff *et al.* 1995, Agren-Cronqvist *et al.* 1996, Bentzen and Overgaard 1996). Unfortunately, there are several misinterpretations of this quantity in the literature, and some published mathematical relationships involve approximations to the true γ. In addition to this, a number of problems exist in estimating the normalized dose–response gradient.

Here, we present a review of the issues involved in quantifying dose–response relationships. Parameterizations will be given for the standard dose–response models in terms of position and steepness. Furthermore, we will clarify the terminology used and discuss some problems involved in estimating the steepness parameter of the dose–response curve. It should be noted that our discussion will be confined to *population* dose–response curves. Other approaches have addressed the influence of heterogeneity in the dose–response of individual patients on the steepness of the population dose–response curve (e.g. Bentzen 1992, Webb 1994, Ågren-Cronqvist *et al.* 1995), but that problem will not be analysed here.

2. Describing the steepness and position of dose–response curves

Mathematically, the steepness θ of a dose–response curve refers to its slope, i.e. the first derivative of the dose–response function, or incidence probability, $P(D)$ with respect to dose D. The slope clearly depends on dose, being greatest in the middle, rising portion of the sigmoid dose–response curve and smaller in the flatter regions closer to 0 and 100% response. Often, the slope is multiplied by 100 to yield the percentage point increase in response per Gy, and this is the convention we use here:

$$\theta = 100\ P'(D) = 100\ \frac{\mathrm{d}P(D)}{\mathrm{d}D}. \qquad (1)$$

As mentioned above, Brahme (1984) introduced the normalized dose–response gradient, γ, as a convenient way to quantify the 'steepness' of the dose–response curve. The normalized dose–response gradient is defined formally as

$$\gamma = D\ \frac{\mathrm{d}P(D)}{\mathrm{d}D} = D\ P'(D). \qquad (2)$$

Thus γ is the product of slope and dose, and is a dimensionless quantity representing the increase in response in percentage points with a 1% increase in dose.

Like the slope, θ, γ depends on dose and attains its maximum value in the middle, rising portion of the dose–response curve. However, the point along the dose–response curve at which γ has its maximum value, γ_{max}, is to the right of the point at which the slope is maximal, with θ_{max}. In the literature, however, many authors have failed to distinguish between these two doses, which we denote here by $D_{\gamma max}$ and $D_{\theta max}$, respectively. In addition, the phrase 'maximum steepness' has been used ambiguously, referring sometimes to θ_{max} and sometimes to γ_{max}.

Further confusion arises from the fact that all of these quantities (θ_{max}, γ_{max}, $D_{\theta max}$, and $D_{\gamma max}$), as well as position parameters such as D_{37} and D_{50} and γ at those doses (γ_{37} and γ_{50} respectively) are dependent on the mathematical model used to describe the dose–response curve. This problem is also addressed in the present paper.

3. Mathematical models of dose–response relationships

3.1. *The Poisson model*

In 1961, Munro and Gilbert derived a mathematical model of tumour dose–response from a set of very simple assumptions. This model, called the Poisson model, has been and still remains extremely influential in radiobiology and radiotherapy. Munro and Gilbert assumed that only tumours with no surviving clonogens at the end of treatment are controlled, and that after irradiation of a population of identical tumours the number of surviving clonogens has a Poisson distribution from tumour to tumour. Further, they assumed that the average surviving fraction of clonogens after a total dose D could be estimated from a log–linear cell-survival curve. These assumptions led them to the model

$$P(D) = \exp[-K\ SF] = \exp[-\exp(\ln K - D/D_0)] \qquad (3)$$

where K is the initial number of clonogens, SF is the surviving fraction of clonogens after irradiation, and D_0 is a parameter describing the radiosensitivity of the clonogens.

It is often convenient to reparameterize the Poisson model, rewriting it so that the parameters K and D_0 are replaced by quantities more directly related to the observed dose–response data. For example, the Poisson dose–response model can be reparameterized in terms of the dose required for a response level of 1/e (≈37%), D_{37}, and the value of the normalized dose response gradient at this level, γ_{37}:

$$P(d) = \exp\left[-\exp\left\{ e\ \gamma_{37} \left(1 - \frac{D}{D_{37}} \right) \right\} \right]. \quad (4)$$

Alternatively, the Poisson model can be parameterized in terms of D_{50} and γ_{37} as given in Table 1. The motivation for using γ_{37} in the parameterization is given in §4.

3.2. *The logistic model*

This is a standard model used in a variety of statistical applications and standard software for estimating the parameters of this model, so-called logistic regression, is available in many statistical software packages. In radiobiology this model came into widespread use after the work by Suit and colleagues (1965). The idea of the model is to write the probability of an event as

$$P = \frac{\exp(u)}{1 + \exp(u)}, \quad (5)$$

where, when analysing data from fractionated radiotherapy, u has the form

$$u = a_0 + a_1\ D + a_2\ D\ d. \quad (6)$$

Here, D is total dose and d is dose per fraction, and the representation of the effect of dose–fractionation in this way is of course inspired by the linear–quadratic model (Herring 1980). When treating with a fixed dose per fraction, the two last terms on the right-hand-side become proportional and equation 6 becomes $u = a_0 + (a_1 + a_2 d)\ D = a_0 + b\ D$. In this case, the logistic dose–response curve can be parameterized in terms of γ_{50} and D_{50} (Table 1).

3.3. *The probit model*

Holthusen noted that the empirical dose–response relationship resembles the cumulative distribution functions (CDF) known from statistics, and he even interpreted the derivative of the dose–response function as the density function for the clinical radiosensitivities in a population of patients, as it would be if the dose–response curve were in fact a CDF. He did not attempt to fit one of the standard CDFs to his data. This approach has been used by subsequent authors, usually assuming a normal distribution of the radiosensitivities (Herring 1975, Svensson *et al.* 1975, Metz *et al.* 1982, Lyman 1985). This leads to the so-called probit model. Lange and Gilbert (1968) used this dose–response model as a computationally convenient approximation to the Poisson model. Theoretically, the probit model is attractive for studying the effect of multiple independent sources of variation in dose delivery and radiosensitivity, e.g. combined dosimetric uncertainty and biological variability in sensitivity (Herring 1975, Svensson *et al.* 1975).

3.4. *Using the logarithm of dose as the covariate*

Suit *et al.* (1965) proposed using the logarithm of dose, rather than dose, as the covariate in the logistic

Table 1. Parameterizations of the three most frequently used dose–response models in terms of the dose for 50% response, D_{50}, and the normalized dose–response gradient, γ

	Dose as covariate	Logarithm of dose as covariate
Poisson	$\exp\left[-(\ln 2)^{\left(\frac{D}{D_{50}}\right)} \exp\left\{ e\ \gamma_{37} \left(1 - \frac{D}{D_{50}} \right) \right\} \right]$	$2^{-\left(\frac{D_{50}}{D}\right)^{4\gamma_{37}}}$
Logistic	$\frac{1}{1 + \exp\left[4\ \gamma_{50} \left(1 - \frac{D}{D_{50}} \right) \right]}$	$\frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{4\gamma_{50}}}$
Probit*	$\frac{1}{2}\left(1 - \mathrm{Erf}\left[\gamma_{50}\sqrt{\pi} \left(1 - \frac{D}{D_{50}} \right) \right] \right)$	$\frac{1}{2}\left(1 + \mathrm{Erf}\left[\gamma_{50}\sqrt{\pi} \ln\left(\frac{D}{D_{50}} \right) \right] \right)$

*The error function is defined as $\mathrm{Erf}(z) = 2/\sqrt{\pi} \int_0^z \exp(-u^2) \mathrm{d}u$.

dose–response relationship, i.e.

$$u = a_0 + b \ln(D) \quad (7)$$

in equation 6. This suggestion sprang from the impression that experimental animal data were more adequately described when dose was logarithmically transformed. Mathematically, it has the advantage that the predicted response probability $P(D)$ goes to zero as D goes to zero (Herring 1980). This is in contrast to the formulation with D as covariate where $P(0)$ typically will be very small but nonetheless greater than zero, although this is rarely a problem in practice. Goitein (1979) also used $\ln(D)$ rather than D as a covariate in the probit dose–response model. To our knowledge, the logarithm of dose has not been used as a covariate with the Poisson model. According to the mechanistic interpretation of the Poisson model, the logarithmic transformation of dose would mean that the surviving fraction of irradiated cells would be a linear rather than an exponential function of dose, which is not consistent with a wealth of experimental data. Empirically, however, the Poisson model with covariate $\ln(D)$ is a sigmoid curve that can be fitted to dose–response data (see section 5). Table 1 gives the parameterizations of the dose–response curves with $\ln(D)$ as the covariate for the logistic, the probit and the Poisson models. Any reference to the three models in this paper is to the form with dose as the covariate unless explicitly stating otherwise.

3.5. *The parameterization of the Poisson model proposed by Källman* et al.

The Stockholm group (Källman *et al.* 1992, Agren-Cronqvist *et al.* 1995, 1996) has frequently used the following dose–response model in their data analyses:

$$P(D) = 2^{-\exp[e\,\gamma_S(1-(D/D_{50}))]}. \quad (8)$$

Although they refer to this model as the Poisson model, it is an *approximation* to the Poisson model. In fact, the parameter γ_s appearing in equation 8 does not actually represent a normalized dose–response gradient, since γ_s is larger than the true γ (calculated from equation 2) at any point on the dose–response curve described by their equation.

The interpretation of γ_s as a normalized dose–response gradient has a practical consequence: if the model published by the Stockholm group (equation 8) is used for empirical fitting of dose–response data, the true maximal γ will be overestimated. Interestingly, it is possible to derive an exact expression for the discrepancy between γ_s and the parameter γ_{37} from the Poisson model of equation 4. If two arbitrary sets of coordinates are fixed on the dose–response curve, it can be shown that

$$\gamma_S = \gamma_{37,p} - \frac{\ln(\ln 2)}{e} \approx \gamma_{37,p} + 0{\cdot}135 \ldots \quad (9)$$

The relative size of this error depends on the steepness of the dose–response curve but increases from 7 to 14% as γ decreases from 2 to 1, i.e. in the typical range seen for human tumours of the head and neck. Numerically, this bias is relatively modest as compared with the typical uncertainty in the estimates of dose–response parameters. Yet, it should be realized that the parameterization is mathematically wrong.

Källman *et al.* (1992) also published a parameterization in terms of position and steepness for the logistic model. Note that their formula is for the logistic model using $\ln(D)$ rather than D as covariate, a circumstance that was not clearly specified in their paper.

4. Relationships among the various steepness measures

As mentioned above, the point at which the dose–response curve attains its maximum slope, is not the same as the point at which the normalized dose–response gradient, γ, is maximized. For example, the Poisson dose–response curve with covariate D has its maximum slope at the 1/e level, i.e. at D_{37}. However, γ_{max} is attained at a dose $D_{\gamma max} > D_{37}$, and is typically a few percent larger than at the 1/e level. Figure 1

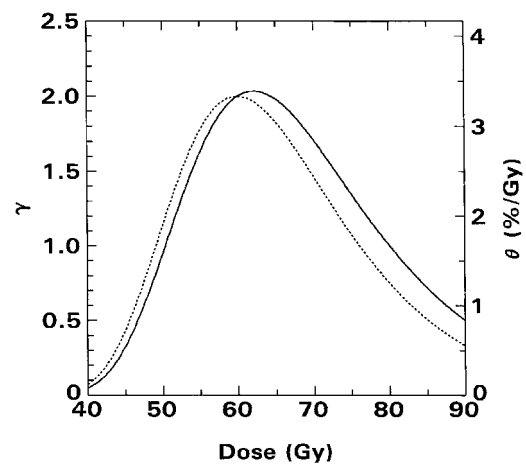

Figure 1. Plot of the normalized dose–response gradient γ (solid curve; left ordinate axis) and the dose–response slope θ (stippled curve; right ordinate axis) as a function of dose for a Poisson dose–response model (covariate D) with $\gamma_{37}=2$ and $D_{37}=60$ Gy (Table 1). The scales for the two vertical axes were chosen so that the plotted curves intersect at $D=60$ Gy, which corresponds to the peak value of the dose–response slope. The maximum γ is attained to the right of this point, at $D \approx 62{\cdot}2$ Gy, and $\gamma_{max} > 2$, about 2·04.

shows this point for a Poisson dose–response curve with $D_{37}=60$ Gy and $\gamma_{37}=2$. The maximum dose–response slope, θ_{max}, is attained at $D=60$ Gy and is approximately 3·3%/Gy $(=\gamma_{37}/D_{37}\,100)$. In contrast, $D_{\gamma^{max}}\approx 62{\cdot}2$ Gy, $P(D_{\gamma^{max}})\approx 43{\cdot}9\%$, and $\gamma_{max}\approx 2{\cdot}035$.

Both the logistic and the probit models with dose as covariate attain their maximum dose–response slope at the 50% level but $D_{\gamma^{max}}$ is to the right of this dose. In contrast, when $\ln(D)$ is used as covariate, $D_{\gamma^{max}}=D_{37}$ for the Poisson model and $D_{\gamma^{max}}=D_{50}$ for the logistic and the probit models, and $D_{\theta^{max}}$ is to the left of these points in each case. These relationships are summarized in Table 2.

Which steepness measure should be reported? A simple convention for specifying the steepness of the dose–response curve could be to give γ_{max} or θ_{max}. However, as shown by Brahme (1984), there is a particularly simple relationship between $\ln K$ in the standard formulation of the Poisson model and γ at the dose $D_{\theta^{max}}$, i.e. at the 37% response level:

$$\gamma_{37,P}=\frac{\ln K}{e}. \tag{10}$$

Under the assumption of a linear–quadratic cell-survival curve, this equation still holds up if the dose–response curve is generated by varying the number of constant size dose fractions. In other words: the normalized dose–response gradient at the point of maximum steepness of the dose–response curve is independent of dose per fraction, on the position of the dose–response curve, and on the fractionation parameters of the linear–quadratic model, α and β. A similar relationship holds up for the logistic model, again provided that the dose per fraction is held constant, and also here the relevant γ is the value at $D_{\theta^{max}}$:

$$\gamma_{50,L}=-\frac{a_0}{4}. \tag{11}$$

There is one caveat here, namely that $\ln K$ or a_0 should be the effective values of these parameters; that is, they should include all the covariates that do not depend on dose. Thus, other clinical factors, like tumour volume, or treatment characteristics, like overall treatment time, will modify these constants.

The simple property shown in equations 10 and 11 motivates the interest in γ at the steepest part of the dose–response curve, and in the literature these are the values usually compiled. Note that for a dose–response curve generated by keeping the number of dose fractions fixed (rather than the dose per fraction) equation 10 or 11 no longer holds up. This is briefly discussed in section 7.

As the maximum steepness is at the 37% response level for a Poisson curve and at the 50% response level for the logit and the probit curves, it is of interest to establish the relationship between γ_{37} and γ_{50} for a Poisson dose–response curve. We find that

$$\gamma_{50,P}=\frac{\ln(2)}{2}\,[e\;\gamma_{37,P}-\ln(\ln(2))]$$
$$\approx 0{\cdot}942\;\gamma_{37,P}+0{\cdot}127\,. \tag{12}$$

It is seen that $\gamma_{50,P}\approx\gamma_{37,P}$ for $\gamma_{37,P}\approx 2{\cdot}19$. The relative difference between $\gamma_{50,P}$ and $\gamma_{37,P}$ is less than 4% for $\gamma_{37,P}$ in the range 1·3–7, which covers many of the clinical γ values.

The Stockholm group also considered the relationship between $\gamma_{50,P}$ and $\gamma_{37,P}$ (Agren-Cronqvist *et al.* 1996) but they arrived at an approximate relationship because of the use of the approximation to the Poisson model.

5. Model dependence of steepness and position parameters

The model dependence of the estimated dose–response parameters varies with the range of data available. First consider the case in which two points in the mid-region of the dose–response curve are specified, say, D_{37} and D_{50}. This corresponds to a situation where the steep part of the curve is very well defined by the data. In this case, the maximum relative difference in the γ_{50} estimates for the various models is about 10% for γ in the typical range 1–4.

Table 2. Relationship between the doses for the maximum dose–response slope, θ_{max}, and the maximum normalized dose–response gradient γ_{max}

	Dose as covariate		Logarithm of dose as covariate	
	Dose for maximum steepness	Dose for maximum γ	Dose for maximum steepness	Dose for maximum γ
Poisson	$D_{\theta^{max}}=D_{37}$	$D_{\gamma^{max}}>D_{37}$	$D_{\theta^{max}}<D_{37}$	$D_{\gamma^{max}}=D_{37}$
Logistic	$D_{\theta^{max}}=D_{50}$	$D_{\gamma^{max}}>D_{50}$	$D_{\theta^{max}}<D_{50}$	$D_{\gamma^{max}}=D_{50}$
Probit	$D_{\theta^{max}}=D_{50}$	$D_{\gamma^{max}}>D_{50}$	$D_{\theta^{max}}<D_{50}$	$D_{\gamma^{max}}=D_{50}$

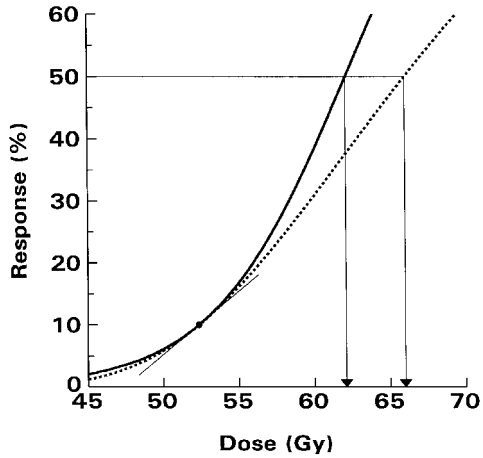

Figure 2. Logistic (thick line) and Poisson (stippled line) dose–response curves with identical D_{10} and γ_{10}. The two curves have a common tangent (thin line) at the 10% level (filled circle). Arrows indicate the D_{50} of the two models.

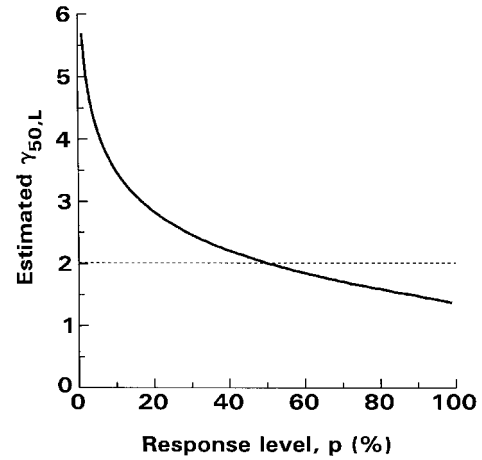

Figure 3. Model-dependence of the estimated γ_{50}. It is assumed that the true dose–response curve is a Poisson curve with $D_{50}=66$ Gy and $\gamma_{37}=2$. The γ_{50} is estimated for a logistic dose–response curve that intersects the Poisson curve at the response level, p, and has the same slope at that point as the Poisson curve. The stippled line corresponds to γ_{50} for the Poisson curve, which is about 2·011. See also Figure 4.

Thus, in this situation the model-dependence of the γ estimate is modest.

Model-dependence becomes more of a problem at the very low response rates and to a lesser extent also at very high response probabilities, where the shapes of the dose–response curves differ markedly. An illustration of this may be obtained by considering the two most frequently used dose–response models, the Poisson and the logistic. Let us assume that we know the 'true' dose–response model, say, a Poisson model with $\gamma_{37}=2{\cdot}0$ and $D_{50}=66$ Gy. Assume further that we want to estimate the parameters of a logistic dose–response model that provides a *locally identical fit* to a set of dose–response data at response level r. This means that the two models should have the same D_r and the same tangent at that point, i.e. the same γ_r (Figure 2). This situation would arise if available response data were concentrated around the level r and provided a reliable estimate of the dose D_r and the steepness of the dose–response curve at that point. Figure 2 shows an example with $r=$ 10%: the estimated γ_{50} for the corresponding logistic curve is much higher than for the Poisson curve, and the D_{50} for the logistic curve is several Gray below that of the Poisson curve.

The differences in the steepness and position parameters of the two curves depend on the level of response at which the two curves are required to agree. Figure 3 shows the estimated γ_{50} of the logistic model as a function of the response level. Very large differences between the steepness of the Poisson and the logistic curve may arise at response levels $<20\%$ and especially at levels $<10\%$. Similarly, the difference between D_{50} (Poisson) and D_{50} (logistic) can be

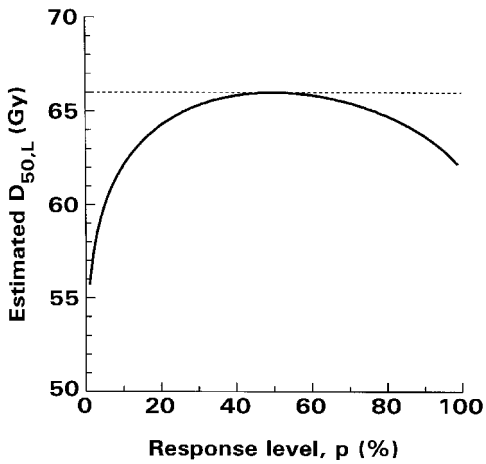

Figure 4. Model-dependence of the estimated D_{50}. It is assumed that the true dose–response curve is a Poisson curve with $D_{50}=66$ Gy and $\gamma_{37}=2$. The $D_{50,L}$ is estimated for a logistic dose–response curve that intersects the Poisson curve at the response level p and has the same slope at that point as the Poisson curve. See also Figure 3.

large (e.g. 10 Gy) for response levels $<10\%$ (Figure 4). Naturally, estimates of D_{50} and γ_{50} derived from dose–response data centered around a very low response level will be very uncertain for statistical reasons. However, this is a separate issue dealt with below.

6. Parameter estimation

Several authors have advocated the use of maximum likelihood estimation (MLE) for estimating the

parameters of dose–response models (Suit *et al.* 1965, Herring 1980, Metz *et al.* 1982, Thames *et al.* 1986). This approach uses the raw data, i.e. the number of subjects and responders at each dose. Statistically, it can be shown that MLE is the optimal method for estimation of dose–response parameters and this method is treated by most standard textbooks in statistics, e.g. Wonnacott and Wonnacott (1977). However, other methods have been applied in the literature, and are in fact necessitated when the raw data are not available. For example, in a comprehensive review of published dose–response data for human tumours, Okunieff and colleagues (1995) used the logistic dose–response model (equation 5) and estimated the model parameters by the least-squares method.

Figure 5 shows an example of how the method of analysis can significantly affect the estimated dose–response parameters. These data are from control of neck nodes with diameter <3 cm in cancer of the pyriform sinus (Bataini *et al.* 1982), with doses plotted at the midpoints of the cited dose ranges, as in the paper by Okunieff and colleagues. Using least-squares analysis, we obtain the estimate $\gamma_{50}=3{\cdot}8$ for the logistic model, in agreement with the value quoted by Okunieff *et al.* (1995). The 95% confidence interval (C.I.) is (2·0, 5·6). The least-squares estimate of γ_{50} is $>50\%$ greater than the value obtained using

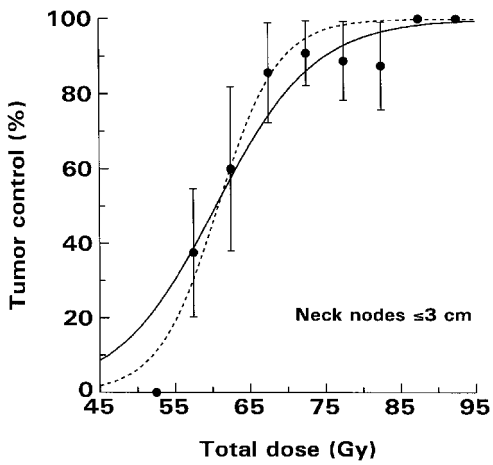

Figure 5. Influence of the method of parameter estimation illustrated by an analysis of the dose–response data from Bataini *et al.* (1982) for control of neck nodes with a maximum diameter $\leqslant 3$ cm (same data as in Figure 7, right panel). Parameters of the logistic model with dose as the covariate have been estimated by the maximum likelihood method (solid line) and the least-squares method (stippled line). Statistically, the latter method gives too much weight to the 0% control observed in two patients receiving <55 Gy. Error bars represent ± 1 SE of the estimated tumour control rate as calculated from the binomial formula.

MLE ($\gamma_{50}=2{\cdot}3$) and in fact lies outside the 95% MLE confidence interval: (0·9, 3·7). The large difference in γ_{50} from the two methods of analysis is mainly due to the influence of the point at 52·5 Gy (0/2 = 0% controlled tumours), which is assigned too much weight by the least-squares method. Of course, the least-squares method could be improved by weighting each dose group to reflect the number of subjects at risk. However, if this information is available, then MLE is to be preferred anyway.

In contrast to the large discrepancy between the two γ_{50} estimates, the D_{50} for the two analyses of the data in Figure 5 are fairly consistent: $D_{50}=60{\cdot}8$ Gy (95% C.I. 58·7–62·8 Gy) for the least-squares analysis versus $D_{50}=60{\cdot}5$ Gy (95% C.I. 54·8–66·2 Gy) for MLE. This is due to the fact that the data span the full range of responses, so the position of the dose–response curve is well resolved. It should be noted, however, that the confidence intervals on D_{50} from the two methods do not agree; the uncertainty in D_{50} is underestimated by the least-squares method.

Another concern is the lack of information on the statistical uncertainty of most γ values published in the literature. Many values are derived from published parameters of multivariate models and estimating the 95% confidence interval for the γ estimate is usually not possible from these reports. In the relatively few cases where confidence intervals have been estimated these are wide, as also illustrated by the example above (see also section 8).

Even in the hypothetical case in which the mathematical form of the dose–response model is known, extrapolation from very low response levels to the 37 or 50% level introduces large uncertainty in both position and steepness estimates. Again, this may be illustrated by an example. Suppose that we wish to estimate γ_{50} from empirical dose–response data observed in two groups of patients treated at two dose levels, 4 Gy apart. Also, assume that the underlying dose–response relationship is a logistic model with $\gamma_{50}=4$ and $D_{50}=66$ Gy. The total number of patients required in the two groups to obtain a 50% standard error of the estimated γ_{50} (i.e. $\gamma_{50}=4\pm 2$) is strongly dependent on the response level (Figure 6). Even at the steepest part of the dose–response curve 72 patients are required to reach this level of precision. This number increases rapidly for response levels lower than about 10% or higher than about 80%.

7. The fractionation effect

Dose–response data are normally obtained either by changing the total dose while keeping the number of fractions constant or by changing the number of

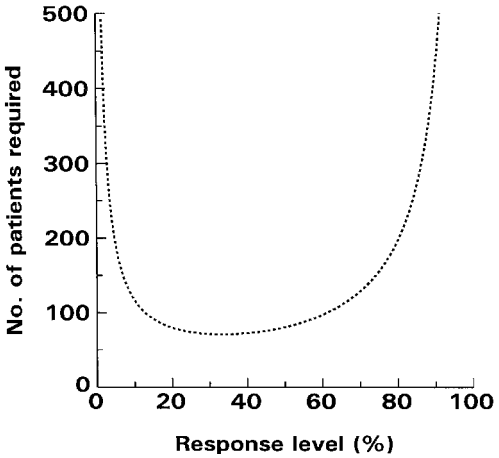

Figure 6. Number of patients required to obtain a 50% SE of the estimated γ_{50} as a function of response level. The underlying dose–response model is assumed to be a logistic model with $\gamma_{50}=4$ and $D_{50}=66$ Gy. The number of patients is estimated for a two-dose group design where the doses are separated by 4 Gy. This number is estimated as a function of the response level at the lower dose.

(constant size) dose fractions. For a specific endpoint, the dose–response curve in the first case is steeper than in the second case and this affects the γ estimate (Brahme 1984, Hendry and Moore 1985, Yaes 1988, Turesson 1991, Bentzen and Overgaard 1993). Biologically, the reason is that with a fixed number of fractions, the increase in dose is accompanied by an increase in dose per fraction (and thereby an increase in biological effectiveness per Gy). This is a reflection of what Withers (1992) called 'double trouble'.

If the cell-survival curve is linear–quadratic in dose, the Poisson model becomes

$$P(D)=\exp\left[-K\exp\left(-\alpha D-\beta D\,d\right)\right]$$
$$=\exp\left[-\exp\left(\ln K-(\alpha+\beta d)D\right)\right]. \qquad (13)$$

When treating with a fixed dose per fraction equation 11 has the same form as equation 3 with $D_0=1/(\alpha+\beta d)$ and equation 10 is still valid. However, when dose is delivered in a fixed number of fractions, the mathematical form of the dose–response model changes (see also Källman *et al.* 1992, Ågren-Cronquist *et al.* 1996). This affects the derivative and thereby the mathematical forms of both γ and θ. The parameterization in Table 1 is then no longer valid because a third parameter (e.g. α/β) is required. Nevertheless, the model in Table 1 may still be used as an approximation but with the relevant γ_{37} for a fixed number of fractions, $\gamma_{37,N}$. A full analysis of this problem is beyond the scope of the present paper, but this is often a very close approximation. The error depends on both α/β and the steepness of the curve. For example, for a Poisson model with 'typical' steepness and position parameters the maximum absolute error in γ for the exact and the approximate dose–response curves is around 0·1 for $\alpha/\beta=3$ Gy and $\gamma_{50,d}=2$, where the index d refers to a dose–response curve generated with a fixed dose per fraction.

For the logistic model, the following relationship can be shown (Bentzen and Overgaard 1996)

$$\gamma_{50,N}=\gamma_{50,d}+\frac{a_2}{4}\frac{D_{50}^2}{N}. \qquad (14)$$

where N is the number of fractions and a_2 is the coefficient defined in equation 6. A similar formula may be derived for the relationship between γ_N and γ_d at other response levels than 50%, but this is omitted here. For the Poisson model, the equivalent of equation 14 is

$$\gamma_{37,N}=\gamma_{37,d}+\frac{\beta}{e}\frac{D_{37}^2}{N}. \qquad (15)$$

8. Analysis of dose–response data, an example

Many of the points discussed here are illustrated by a practical example. We have chosen to re-analyse two of the dose–response data sets published by Bataini *et al.* (1982). One is for local control of T1 + T2 carcinoma of the pyriform sinus and the other is for control of positive neck nodes with maximum diameter ⩽3 cm, from the same primary. The former data set (Figure 7a) is concentrated in the response range 30–70%. In this range, there is very little difference among the dose–response models listed in Table 1. This is also reflected in the position and steepness estimates listed in Table 3. The estimated D_{50} ranges from 62·6 to 63·7 Gy, corresponding to a relative difference of about 1%. The relative difference in the largest and smallest values of γ_{50} and θ_{max} are 11 and 14% respectively. Slightly more variability is seen in the γ_{37} estimates where the relative difference is 16%. Still, the model-dependence of the steepness parameters is modest for this data set.

Figure 7b shows the neck-node data and the maximum likelihood fits of four dose–response models. This data set is concentrated at high control probabilities, which causes a wider spread in the curves, particularly at low response levels. Model parameters are listed in Table 4. Again, the variation in D_{50} is very small with a maximum relative difference of 0·5%. This very low variation is due to the fact that the curves almost cross around the 50% response

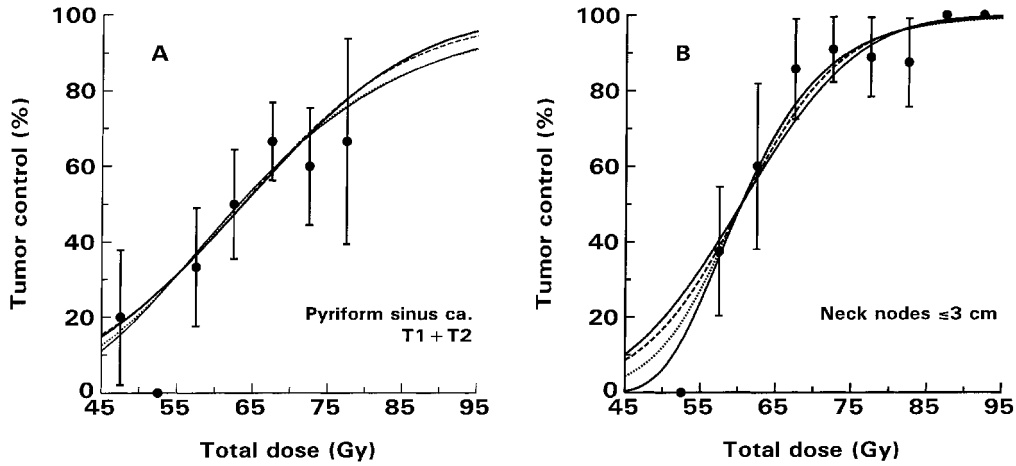

Figure 7. Dose–response data from Bataini *et al.* (1982) for local control of T1 + T2 carcinoma of the pyriform sinus (left panel) and neck nodes with a maximum diameter ⩽3 cm (right panel, same data as in Figure 5). Curves illustrate the fit of four dose–response models to the data: the logistic model with dose as the covariate (stippled line) and with the logarithm of dose as covariate (dotted line), the Poisson model with covariate D (thin solid line), and the probit model with covariate D (thick solid line). Error bars represent ±1 SE of the estimated tumour control rate as calculated from the binomial formula.

Table 3. Dose–response parameters for local tumour control of T1–T2 pyriform sinus carcinoma (data from Batiani *et al.* 1982, table 7)

Model	D_{50} (Gy)	γ_{37}	γ_{50}	γ_{max}	$D_{\gamma_{max}}$ (Gy)	Max slope (%/Gy)
Logistic	63·6 (57·8, 69·5)	1·22	1·45 (0·21, 2·68)	1·49	67·2	2·28
Poisson	63·1 (57·3, 69·0)	1·34	1·39 (0·34, 2·44)	1·39	61·9	2·34
Probit	63·7 (57·8, 69·5)	1·20	1·41 (0·25, 2·57)	1·46	68·4	2·21
Logistic, covar. ln(D)	63·2 (57·3, 69·1)	1·32	1·42 (0·23, 2·61)	1·42	63·2	2·32
Poisson, covar. ln(D)	62·6 (56·5, 68·8)	1·39	1·31 (0·34, 2·29)	1·39	56·8	2·53
Probit, covar. ln(D)	63·2 (57·3, 69·2)	1·30	1·38 (0·27, 2·49)	1·38	63·2	2·28

Table 4. Dose–response parameters for control of neck nodes from pyriform sinus carcinoma with max diameter ⩽3 cm (data from Batiani *et al.* 1982, table 8)

Model	D_{50} (Gy)	γ_{37}	γ_{50}	γ_{max}	$D_{\gamma_{max}}$ (Gy)	Max slope (%/Gy)
Logistic	60·5 (54·8, 66·2)	2·01	2·30 (0·90, 3·71)	2·33	61·9	3·80
Poisson	60·4 (55·9, 65·0)	2·84	2·80 (1·27, 4·33)	2·86	58·7	4·92
Probit	60·4 (53·9, 66·9)	1·75	1·99 (0·80, 3·18)	2·03	62·7	3·29
Logistic, covar. ln(D)	60·4 (55·4, 65·5)	2·45	2·63 (1·23, 4·03)	2·63	60·4	4·39
Poisson, covar. ln(D)	60·2 (56·2, 64·3)	3·33	3·14 (1·59, 4·69)	3·33	57·8	5·80
Probit, covar. ln(D)	60·4 (54·8, 66·0)	2·19	2·32 (1·15, 3·48)	2·32	60·4	3·89

level. The relative differences in γ_{50} and θ_{max} are 58 and 76% respectively and for γ_{37} it is 90%. Among the models with D as covariate, it is seen that the Poisson model provides the highest estimates for all of the steepness parameters. This observation is in qualitative agreement with Figure 3, which shows that γ_{50} (logistic) $< \gamma_{50}$ (Poisson) for dose–response data that defines the high-response-rate end of the curve.

Tables 3 and 4 also show that $\gamma_{max} > \gamma_{37}$ for the Poisson model, and $\gamma_{max} > \gamma_{50}$ for the logistic and the probit models. Using ln(D) as the covariate, $\gamma_{max} = \gamma_{50}$ for the logistic and the probit models and $\gamma_{max} = \gamma_{37}$ for the Poisson model.

9. Discussion and conclusion

As illustrated in this paper, the quantified position and steepness of dose–response curves can depend markedly on the mathematical model used to describe the underlying dose–response relationship. Many authors have preferred the Poisson model because of its apparent biological or mechanistic interpretation (Munro and Gilbert 1961, Porter 1980,

Källman *et al.* 1992, Agren-Cronqvist *et al.* 1996). However, the assumption of a Poisson distribution in the surviving clonogens will be violated in situations where the clonogens proliferate during the course of treatment (Tucker *et al.* 1990, Tucker and Taylor 1996). Furthermore, dosimetric and biological heterogeneities will affect both the parameter estimates and most likely also the shape of the dose–response curve (Fischer and Moulder 1975, Wheldon 1980, Hendry and Moore 1985, Zagars *et al.* 1987, Bentzen *et al.* 1990, Bentzen 1992). Therefore, the straightforward interpretation of parameters in the Poisson model may be dubious. This opens the way for a more pragmatic attitude to the choice of model. In principle, it is an empirical problem to decide which one of the dose–response models discussed here would provide the best description of clinical and experimental dose–response data. In practice, these models are close approximations to one other over a broad range of responses (Lange and Gilbert 1968, Walker and Suit 1981). It is virtually impossible to imagine that a goodness-of-fit statistic, derived from fitting the different models to a set of noisy data, would discriminate among the models in a meaningful way. Statistically, all these dose–response relationships are examples of generalized linear models (McCullagh and Nelder 1989), and although there are statistical reasons for choosing between them depending on the error structure of the data, this criterion is hardly feasible in practice. As for parameter estimation they behave similarly. In the radiobiology and radiation oncology literature there is no consensus on the choice of model, although there may be a tendency to use the Poisson model in tumour-control studies, and the logistic or probit models in analysing normal-tissue complications. This lack of consensus is a problem when comparing steepness estimates as these will be model dependent.

Clinically, the model-dependence of position and steepness parameters for dose–response curves is a major problem for severe complications, which will normally be quite rare. If the underlying dose–response model is a Poisson model, then fitting a logistic curve to data at low response rates may lead to underestimates of tolerance (D_{50} too low) and overestimates of steepness (γ_{50} too high). On the other hand, and this is perhaps more serious, if the underlying dose–response model is a logistic model, fitting a Poisson curve to the data could seriously *over*estimate tolerance and *under*estimate steepness. This could have serious consequences for example in the design of dose escalation protocols.

Most γ values in the literature are quoted without any estimate of its statistical uncertainty. To establish meaningful conclusions on the steepness of the dose–response curves for various endpoints, confidence intervals or standard errors of the estimates are needed. Statistical uncertainty is a particular problem with estimation from low-incidence data. As shown above, very large clinical series are required to estimate the normalized dose–response gradient at the steepest part of the dose–response curve with a reasonable precision from incidence data around 10%.

In summary, this paper has reviewed the ambiguities associated with quantifying the steepness and, to a somewhat lesser extent, the position of radiation dose–response curves. These sources of ambiguity include the model-dependence of the estimated parameters, the use of various descriptors of 'steepness', the influence of whether a fixed dose per fraction or a fixed number of fractions was used in generating the data, the method of parameter estimation, and the failure of many authors to report the statistical uncertainty of cited parameter values. In view of the clinical significance of obtaining accurate quantitative descriptions of radiation dose–response relationships, it is important that published reports endeavour to minimize these ambiguities. Specifically, published estimates of the steepness of dose–response curves should be accompanied by clear descriptions of the nature of the data (e.g. treatment schedule), the mathematical model used to analyse the data, the method of analysis, the parameter being estimated, and a measure of the uncertainty in the reported estimate.

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