Generalization of the Normalized Dose-response Gradient to Non-uniform Dose Delivery

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A generalization of the standard dose-response gradient to arbitrarily heterogeneous dose distributions has been developed. The generalized dose-response gradient is the scalar product of the vector representing the dose distribution and the gradient of the dose-response relation with respect to that dose vector. It is shown that, for a tumor, the individual γ-values for each portion of the tumor divided by the corresponding local tumor control probability should be added to get the total value for the heterogeneously irradiated tumor. This corresponds to summing up the contributions of all tumor volumes so that the total value of the gradient is related to the logarithm of the total tumor clonogen number. General expressions are also derived for the change in the dose-response relation as a function of a change in the delivered dose distribution.

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There is an increasing need to better quantify the shape of the dose-response relation observed in radiation therapy. This need pertains to the shape of the normal tissue response curve at low doses near the onset of complications as well as the shape of the tumor cure curve at high doses and control probabilities, but also with regard to the steepness and the exact location of the response curve along the dose axis. Early on, this was described by giving D_5 and D_{50} doses where 5 and 50%, respectively, of the patients experienced the complication in question (1). For tumor control, the major interest is for the curve shape at medium to high doses to quantify the increase in local tumor control probability as it slowly approaches unity at high doses. The increasing need for this kind of data is due to the fact that new types of treatment optimization algorithms are rapidly becoming available in treatment planning and they are capable of maximizing the treatment outcome based on the exact shape of clinically observed dose-response relations and radiobiological models. Therefore, it is becoming increasingly important to collect accurate clinical dose-response data.

When uniform dose delivery is used, it may be intuitive to measure the slope or steepness of the dose-response relation in absolute units such as %/Gy. However, since non-uniform dose delivery is used more and more to get an increased therapeutic effect and dose to the gross tumor, a somewhat lower dose to the microscopic tumor spread and the lowest possible dose to organs at risk, it is more relevant from a scientific point of view to use the normalized dose-response gradient to quantify the dose-response relation. For example, if we want to quantify the amount of double trouble (2), or double advantage for that matter, when biologically optimized intensity-modulated dose delivery is used to decrease the dose to normal tissues, we will have to multiply the relative dose increase or decrease respectively with the normalized dose-response gradient γ to get the relative increase or decrease in complication probability or tumor control (3–5).

Historically, a large number of steepness concepts have been used in addition to D_5 and D_{50}, as mentioned above. Some authors used the dose increase to get from 25% to 50% complications for normal tissue and from 50% to 75% tumor control for tumors to get clinically interesting steepness figures (6). Several authors have used σ, the standard deviation in an apparent threshold dose, related to the width of the steep sigmoidal portion of the dose-response relation (7–10). It is straightforward to show that the relative apparent standard deviation is approximately related to γ through $\sigma \approx \bar{D}/(\gamma\pi\sqrt{2})$, where $\bar{D}$ is the mean dose. However, this is no real standard deviation since its value is linked to the probability and extreme randomness as associated with the eradication of the last few clono-

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gens, and thus independent of how well we know the exact sensitivity of the patient. Other authors using the logistic model often use its steepness parameter k which is related to γ through $\gamma = k/4$ (5), while many authors use various absolute measures (cf. (11)). In this paper we illustrate the high clinical value of a suitable general normalized measure of the steepness of the dose-response relation.

METHODS AND DEFINITIONS

Uniform dose delivery

The concept of a normalized dose-response gradient, γ, was introduced some 15 years ago (3) and has become a convenient tool for the characterization of a tissue and its dose-response relation for both tumors and healthy normal tissues. The normalized response gradient $\gamma(D)$ can be defined at any dose level D according to

$$\gamma(D) \equiv D\left(\frac{\mathrm{d}P(D)}{\mathrm{d}D}\right) \qquad [1]$$

where $P(D)$ is the dose-response relation for the tissue at hand. When $P(D)$ is known, this expression can be used to calculate the normalized steepness of the dose-response relation, that is the ratio of the percental increase in response for one percent increase in dose at any dose level D from zero to infinity. One of the most attractive features of the γ definition above is that it can be used to predict the change in response from a small change in dose according to

$$\Delta P(D) \approx \frac{\Delta D}{D}\gamma \qquad [2]$$

Recent discussions on the clinical usefulness of γ-values have been published by several authors (5, 11–13). Alternatively, one can also use the γ definition to calculate the normalized steepness at a given probability level of response through the relation $\gamma_P = \gamma(P) = \gamma(P(D))$. A particularly useful value from a biological point of view is the value of $\gamma(D)$ at the dose $\tilde{D}$, where the absolute dose-response gradient is steepest; that is

$$\tilde{\gamma} \equiv \tilde{D}P'(\tilde{D}), \text{ where } P'(\tilde{D}) = \max_D\left\{\frac{\partial P(D)}{\partial D}\right\} \qquad [3]$$

Assuming Binomial statistics this happens at $P = (1-1/N_0)^{N0}$, where N_0 is the initial number of clonogens or functional subunits (14). Within the limit of $N_0 \to \infty$, (the Poisson approximation), it is recognized that P besides the minus sign is identical to the definition of e, the base of the natural logarithm, and thus $P = 1/e \approx 37\%$. The value of γ at this point is particularly important since it depends only on the initial number N_0 of clonogens or functional subunits. The γ-value according to Equation [3] is given as $\tilde{\gamma} = (1-1/N_0)^{N_0-1}$ and $\tilde{\gamma} = \ln N_0/e$ for Binomial and Poisson statistics, respectively. When $\tilde{\gamma}$ has been determined clinically it can thus be used to calculate the effective number $N_{0,\mathrm{eff}}$ of clonogens in a tumor. Since most tumors contain both well-oxygenated and hypoxic cells and sometimes also tumor clones of different intrinsic radiation sensitivity, and it is often the most resistant clone that determines the response of the tumor (5). The clinically observed γ-value therefore corresponds to the weighted effective clonogen number, depending on the number of clonogens and their respective sensitivity. This value is influenced mainly by the most resistant clonogens, since they will generally determine the high-dose behavior of the dose-response relation.

The highest possible relative steepness of the normalized dose-response relation is by definition given as:

$$\hat{\gamma} = \max_D\left\{D\frac{\partial P(D)}{\partial D}\right\} \qquad [4]$$

$\hat{\gamma}$ is the maximum value of the normalized dose-response gradient, and as such can be used to describe the typical shape of the dose-response relation and to estimate extreme conditions, for example with regard to accuracy requirements. In general, $\hat{\gamma}$ is only slightly larger than $\tilde{\gamma}$; for the Poisson model the difference is seldom more than $100/(2e\tilde{\gamma}^2) \approx 1\%$ (5). Furthermore, clinically determined γ-values are often imprecise, with a standard deviation of more than 10% (15). Therefore, in most clinical situations it is not important to distinguish between $\tilde{\gamma}$ and $\hat{\gamma}$, and generally sufficient to use the notation γ when the risk of any misunderstanding or error is negligible (cf. (3)). It should be pointed out that the above definitions are general and do not depend on a particular dose-response model. However, under simplifying assumptions on cell survival statistics such as Probit, Logit, Poisson or Binomial survival, the shape of the function $\gamma(D)$ depends on one single parameter such as the number of clonogens N_0 or the value γ at a given control level. These definitions and most dose-response relations implicitly assume a homogeneous dose distribution $D(\boldsymbol{r}) = D$ and uniform radiation sensitivity throughout the relevant organ volume. In the present paper we show how the γ-value definition can be generalized for non-uniform dose delivery.

Non-uniform dose delivery

A general dose distribution $D(\boldsymbol{r})$ will from here on be denoted by the vector notation $\boldsymbol{D}$. With this notation a dose response-relation $P(D(\boldsymbol{r})) = P(\boldsymbol{D})$ can be viewed as a functional or mapping $P{:}S \subset R^n \to R^1$ that maps the n-dimensional dose vector $\boldsymbol{D}$ onto a scalar quantity P describing the probability of response for an arbitrary, non-uniform, dose distribution.

The D_{50} and D_{37} concepts. The dose D_{50} is the dose where 50% of the patients experience response, i.e. either complications or tumor control, and is commonly used to specify clinical response levels (1). D_{50} can readily be

expressed in terms of D_0 and N_0 when using the Poisson model (5) as:

$$D_{50} = D_0(\ln N_0 - \ln\ln 2) = D_0(e\tilde{\gamma} - \ln\ln 2) \quad [5]$$

Similarly, one can derive for the Binomial model:

$$D_{50} = D_0 \ln\left(\frac{2^{1/N_0}}{2^{1/N_0}-1}\right) \quad [6]$$

An alternative and equally useful concept is D_{37}, the dose where $1/e$ or 37% of the patients experience a certain response or precisely one clonogen on average survives. This readily defined concept becomes particularly simple for the Poisson model (cf. (16)):

$$D_{37} = D_0 \ln N_0 \quad [7]$$

The expression for D_{37} when using the Binomial model similarly becomes

$$D_{37} = D_0 \ln\left(\frac{e^{1/N_0}}{e^{1/N_0}-1}\right) \approx D_0 \ln\left(\frac{N_0}{1+\frac{1}{2N_0}}\right) \quad [8]$$

For large N_0, these expressions agree well as expected.

The D_{eff} concept. Since the definitions for the γ-value given above assume a homogeneous dose distribution, an obvious approach to handle non-uniform doses would be simply to introduce the mean dose $\bar{D}$ in the formulas. If the dose variance is low, this can be a rather good approach as shown in (3). The tumor response $P_B(\boldsymbol{D})$ can to the second order be approximated as:

$$P_B(\boldsymbol{D}) \approx P_B(\bar{D}) - \frac{\gamma^2}{2P_B(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2 \quad [9]$$

where the $\sigma_D/\bar{D}$ is the coefficient of variation of the dose distribution in the tumor. The negative sign of the quadratic term in equation [9] shows that all variations in the dose distribution that introduce deviations from the mean dose level reduce the control probability for a given mean tumor dose $\bar{D}$. This should be expected, as the decreased survival in low-dose areas can never be completely compensated by the increased survival in high-dose areas. As shown in (17) it is even possible based on equation [9] to define an effective uniform dose, D_{eff}:

$$D_{\text{eff}} = \bar{D}\left[1 - \frac{\gamma}{2P_B(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2\right] \quad [10]$$

A similar concept, called *EUD*, was introduced in the study by Niemierko (18), and the present authors recently generalized both these concepts one step further by equating the tumor control at a uniform dose $\bar{\bar{D}}$ to the real value with non-uniform dose delivery to the gross tumor and the lymphatic spread (19).

The use of $\bar{\bar{D}}$, D_{eff} or *EUD* in the definitions for γ above is in most circumstances a good enough approximation when the dose variations in terms of, for example, the standard deviation σ_D are not too large.

The generalized normalized dose response gradient. A more general approach to handling arbitrary non-uniform dose distributions is explicitly to define γ as a function of any dose distribution $\gamma(\boldsymbol{D})$. One natural way to generalize γ along this line of thought is to replace the derivative in equation [1] with a gradient as

$$\gamma(\boldsymbol{D}) = \boldsymbol{D}\cdot\nabla_{\boldsymbol{D}}P(\boldsymbol{D}) = \sum_{i=1}^{n} D_i \frac{\partial P(\boldsymbol{D})}{\partial P_i}\frac{\partial P_i(\boldsymbol{D})}{\partial D_i} = \sum_{i=1}^{n}\frac{\partial P(\boldsymbol{D})}{\partial P_i}\gamma_i \quad [11]$$

where D_i is the quasi-uniform dose in voxel i, and γ_i, the local contribution to the normalized dose-response gradient from each voxel i is given as

$$\gamma_i = \gamma(D_i) \equiv D_i \frac{\partial P_i(\boldsymbol{D})}{\partial D_i} \quad [12]$$

Thus the sum of all local normalized response gradients can be viewed as a scalar product between the dose vector and the gradient of the response function with respect to the dose vector. This is a natural generalization since for each voxel the local γ-value, γ_i, will be related to the local number of clonogens or FSUs (Functional Sub-Units) and thus the organ-specific value will be related to the weighted sum over all voxels.

In accordance with equation [3] the normalized dose-response gradient at the steepest absolute point for non-uniform dose delivery is given as

$$\tilde{\gamma} \equiv \tilde{\boldsymbol{D}}\cdot\nabla_{\boldsymbol{D}}P(\tilde{\boldsymbol{D}}), \text{ where } \nabla_{\boldsymbol{D}}P(\tilde{\boldsymbol{D}}) = \max_{\boldsymbol{D}}\left\|\nabla_{\boldsymbol{D}}P(\boldsymbol{D})\right\| \quad [13]$$

This equation is also a way to define the effective clonogen number (see the text below equation (3)) using non-uniform dose delivery and assuming Poisson statistics:

$$N_{\text{eff}} = \exp(e\tilde{\gamma}). \quad [14]$$

If there is a heterogeneous distribution of radiosensitivity within each voxel, the effective number of clonogens N_{eff} can still be calculated by equation [14] using an appropriate expression for P_B (see (16) for a more detailed discussion on heterogeneous tissues).

Similar to the correspondence between equation [3] and equation [13], an equation corresponding to equation [4] may be defined for heterogeneous dose delivery. The highest possible normalized gradient is thus given as

$$\hat{\gamma} \equiv \max_{\boldsymbol{D}}\{\boldsymbol{D}\cdot\nabla_{\boldsymbol{D}}P(\boldsymbol{D})\} \quad [15]$$

This expression can be effectively evaluated using equation [11] above.

The γ and P_+ value for multiple target volumes and normal tissues

Tumors. When the control probabilities $P_B^j(\boldsymbol{D})$ of n different tumor compartments (j) are all statistically independent, the total probability $P_B(\boldsymbol{D})$ of controlling all of

the n tumor compartments is given as

$$P_{\mathrm{B}}(\boldsymbol{D}) = \prod_{j=1}^{n} P_{\mathrm{B}}^{j}(\boldsymbol{D}) \quad [16]$$

Using the definition [11] and the chain-rule we get (16)

$$\gamma(\boldsymbol{D}) = \sum_{i=1}^{n} \gamma_i(\boldsymbol{D}) \prod_{j \neq i}^{n} P_{\mathrm{B}}^{j}(\boldsymbol{D}) = P_{\mathrm{B}} \sum_{i=1}^{n} \frac{\gamma_i(\boldsymbol{D})}{P_{\mathrm{B}}^{i}(\boldsymbol{D})} \quad [17]$$

where $\gamma_i(\boldsymbol{D})$ is the normalized dose-response gradient from equation [11] for tumor compartment i. Thus two tumor compartments will have a total normalized dose-response gradient $\gamma = (\frac{\gamma_1}{P_{\mathrm{B}}^{1}} + \frac{\gamma_2}{P_{\mathrm{B}}^{2}})P_{\mathrm{B}}$ (cf. (5)).

Normal tissues. First, let us assume that the injury of at least one normal tissue compartment is sufficient to cause a global injury, and that the compartments individual injury probabilities are statistically independent. Then the total probability $P_{\mathrm{I}}(\boldsymbol{D})$ of global injury is given as

$$P_{\mathrm{I}}(\boldsymbol{D}) = 1 - \prod_{j=1}^{n} (1 - P_{\mathrm{I}}^{j}(\boldsymbol{D})) \quad [18]$$

where n is the number of tissue compartments.

Using the definition in equation [11] above and the chain-rule, we similarly get

$$\gamma(\boldsymbol{D}) = (1 - P_{\mathrm{I}}(\boldsymbol{D})) \sum_{i=1}^{n} \frac{\gamma_i}{1 - P_{\mathrm{I}}^{i}(\boldsymbol{D})} \quad [19]$$

Thus two healthy tissues will have a total normalized dose-response gradient $\gamma = (\frac{\gamma_1}{1 - P_{\mathrm{I}}^{1}} + \frac{\gamma_2}{1 - P_{\mathrm{I}}^{2}})(1 - P_{\mathrm{I}})$.

The probability of complication-free tumor control. In order to optimize treatments we need an objective function which ideally should measure the treatment outcome in terms of the quality of life. A fairly simple but still powerful such scalar quantity is P_+, the probability of tumor control without severe injury. It can be formulated in terms of the probability of tumor control, P_{B}, and the probability of severe injury to healthy tissue, P_{I}, as

$$P_+ = P_{\mathrm{B}} - P_{\mathrm{B} \cap \mathrm{I}} \quad [20]$$

If the probabilities of tumor control and normal tissue injury are independent, the probability of complication-free tumor control will be given as

$$P_+ = P_{\mathrm{B}}(1 - P_{\mathrm{I}}) \quad [21]$$

However, the clinical data, e.g. Ågren et al. (20), suggest that a better approximation is to assume that the probabilities are dependent in the way that fatal injury always implies tumor control so that the probability of complication-free tumor control becomes

$$P_+ = P_{\mathrm{B}} - P_{\mathrm{I}} \quad [22]$$

Thus, according to the definition of a derivative, because P_{B} and P_{I} are rather close together along the dose axis, P_+ should be a bell-shaped Gaussian-like curve, since both P_{B} and P_{I} are sigmoidal and can be approximated by cumulative normal distributions.

The normalized dose-response gradient can be shown to be related to P_+ by noting that at the optimum dose $\boldsymbol{D}^*$ the gradient $\nabla_{\boldsymbol{D}} P_+(\boldsymbol{D}^*)$ has to be zero and therefore also, by equation [22], the normalized dose-response gradients for P_{B} and P_{I} have to be the same. Thus, at the optimum dose, $\boldsymbol{D}^*$ in equation [22] in the first approximation describes a derivative of the complication-free tumor control. If the sigmoid response functions P_{B} and P_{I} are described by a cumulative normal distribution (5), the derivative will just be a Gaussian according to

$$P_+(D) \approx P_+^* e^{-\pi\left(\gamma\frac{D - D^*}{D^*}\right)^2} \quad [23]$$

where P_+^* is the maximum probability of complication-free cure. This expression describes the bell-shaped P_+ curve fairly well, at least near the peak since γ_{B} and γ_{I} are the same there. Both ΔP_{B} and ΔP_{I} can be approximated by equation [2]. Thus a relation between the change in response as a function of the change in complication-free cure can by Taylor expansion be derived from the shape of equation [23] near its peak since there

$$P_+^* - \Delta P_+ \approx P_+^* \left(1 - \pi\left(\gamma \frac{\Delta D}{D^*}\right)^2\right) \quad [24]$$

Thus using equation [2] we immediately get

$$\frac{\Delta P_+}{P_+^*} \approx \pi \Delta P_{\mathrm{B}}^2 = \pi \Delta P_{\mathrm{I}}^2 \quad [25]$$

This expression shows that if one can tolerate a small decrease in P_+, say 0.5%, one can substantially decrease the complication probability by as much as 4% or increase the probability of cure. This former fact is of great clinical interest since it allows to some extent a simultaneous maximization of P_+ and a quasi-minimization of P_{I} (cf. (21)).

RESULTS

Quantification of response by dose distribution alterations

The expression for the change in response as a function of the relative change in dose in equation [2] is only valid for uniform dose distributions.

For a non-uniform dose distribution, $P(\boldsymbol{D})$ can be expanded in a Taylor series as

$$P(\boldsymbol{D} + \Delta\boldsymbol{D}) = P(\boldsymbol{D}) + \Delta\boldsymbol{D} \cdot \nabla_{\boldsymbol{D}} P(\boldsymbol{D}) + \frac{1}{2}(\Delta\boldsymbol{D})^{\mathrm{T}} \nabla_{\boldsymbol{D}}^2 P(\boldsymbol{D}) \Delta\boldsymbol{D} + \cdots \quad [26]$$

Keeping the first-order term only and applying the *Cauchy-Bunyakovskii-Schwarz*' inequality, $\|\boldsymbol{x} \cdot \boldsymbol{y}\| \leq \|\boldsymbol{x}\| \|\boldsymbol{y}\|$, the change in response ΔP can be approximated as

$$\Delta P = P(\boldsymbol{D} + \Delta\boldsymbol{D}) - P(\Delta\boldsymbol{D}) \approx P(\boldsymbol{D}) + \left\|\Delta\boldsymbol{D}\right\|\left\|\nabla_{\boldsymbol{D}} P(\boldsymbol{D})\right\| \quad [27]$$

Using the *Cauchy-Bunyakovskii-Schwarz*' inequality in a similar way on [11] gives

$$\left\|\gamma(\boldsymbol{D})\right\| = \gamma(\boldsymbol{D}) \leq \left\|\boldsymbol{D}\right\|\left\|\nabla_{\boldsymbol{D}} P(\boldsymbol{D})\right\| \quad [28]$$

and combining equations [27] and [28] we get

$$\Delta P(\boldsymbol{D}) \leq \frac{\left\|\Delta\boldsymbol{D}\right\|}{\left\|\boldsymbol{D}\right\|}\gamma(\boldsymbol{D}) \quad [29]$$

The original definition of γ (cf. equation [3] or [4]) gives the highest possible γ, which occurs at responses around 37% for Poisson statistics. The estimate of the change of response while using equation [29] will be too conservative for very low and very high response probabilities. In most clinically relevant circumstances, the response probability for normal tissue complications is in the very low region and the responses for tumor control at fairly high probabilities.

In order to obtain a more accurate quantification of the change in response, one should preferably calculate the γ-value as a function of dose $\boldsymbol{D}$ or $P(\boldsymbol{D})$ as in equation [1] or [11]. Assuming Poisson statistics, the response probability for uniform dose is

$$P(D) = \exp(-N_0 e^{-\alpha D}) \quad [30]$$

so that the normalized dose response gradient becomes

$$\gamma(D) = D\frac{\mathrm{d}P(D)}{\mathrm{d}D} = -P(D)\,\alpha D \ln P(D) \quad [31]$$

Since equation [30] gives $\alpha D = \ln N_0 - \ln(-\ln P(D))$ and $\tilde{\gamma} = \ln N_0/e$, we get

$$\gamma(D) = -P(D)\ln P(D)(e\tilde{\gamma} - \ln(-\ln P(D))). \quad [32]$$

In the first approximation, for a small variance in the dose distribution, this holds for non-uniform dose delivery as well. The normalized dose-response gradient for non-uniform doses is thus approximately given as

$$\gamma(\boldsymbol{D}) = -P(\boldsymbol{D})\ln P(\boldsymbol{D})(e\tilde{\gamma} - \ln(-\ln P(\boldsymbol{D}))) \quad [33]$$

The relative change in response as a function of the relative change in dose can thus be approximated as

$$\Delta P(\boldsymbol{D}) \leq -\frac{\left\|\Delta\boldsymbol{D}\right\|}{\left\|\boldsymbol{D}\right\|}P(\boldsymbol{D})\ln P(\boldsymbol{D})(e\tilde{\gamma} - \ln(-\ln P(\boldsymbol{D}))) \quad [34]$$

or alternatively, if the mean dose $\bar{D}$ is known

$$\Delta P(\boldsymbol{D}) \leq -\frac{\left\|\Delta\boldsymbol{D}\right\|}{\left\|\boldsymbol{D}\right\|}P(\boldsymbol{D})\ln P(\boldsymbol{D})\frac{\bar{D}}{D_{50}}(e\tilde{\gamma} - \ln\ln 2) \quad [35]$$

In many circumstances equation [33] can be further approximated as

$$\gamma(\boldsymbol{D}) \approx -P(\boldsymbol{D})\ln P(\boldsymbol{D})e\gamma \quad [36]$$

where exact equality prevails when $P(\boldsymbol{D}) = e^{-1}$. Hence, the approximate relative change in response as a function of the relative change in dose [34] is

$$\Delta P(\boldsymbol{D}) \leq -\frac{\left\|\Delta\boldsymbol{D}\right\|}{\left\|\boldsymbol{D}\right\|}P(\boldsymbol{D})\ln P(\boldsymbol{D})e\gamma \quad [37]$$

Target volume consisting of two compartments

Consider a tumor consisting of two compartments with N_{01} and N_{02} clonogens and with radio-sensitivities α_1 and α_2 receiving doses D_1 and D_2, respectively. Assuming the responses are governed by Poisson statistics, the total response of the tumor will be

$$P(\boldsymbol{D}) = P_1(D_1)P_2(D_2) = e^{-(N_{01}e^{-\alpha_1 D_1} + N_{02}e^{-\alpha_2 D_2})} \quad [38]$$

where $\boldsymbol{D} = (D_1,\ D_2)$.

The gradient of the dose response function is given as

$$\nabla_D P(\boldsymbol{D}) = P(\boldsymbol{D})(\alpha_1 N_{01}e^{-\alpha_1 D_1},\ \alpha_2 N_{02}e^{-\alpha_2 D_2}) \quad [39]$$

and the normalized dose-response gradient according to equations [11] and [17] is thus

$$\gamma(\boldsymbol{D}) = P(\boldsymbol{D})(D_1\alpha_1 N_{01}e^{-\alpha_1 D_1} + D_2\alpha_2 N_{02}e^{-\alpha_2 D_2}) \quad [40]$$

Consider, for example, the case where the doses, clonogen densities, and the responses are homogeneous, i.e. $\boldsymbol{D} = D = D_1 = D_2$, $N_{01} + N_{02} = N_0$ and $\alpha_1 = \alpha_2 = \alpha$, then

$$\gamma(D) = D\alpha N_0 P(D)e^{-\alpha D}. \quad [41]$$

The gradient is maximized for $D = \ln N_0/\alpha$, which in equation [3] gives $\tilde{\gamma} = \ln N_0/e$, which is the familiar expression for the normalized dose-response gradient when using Poisson statistics and uniform dose.

Let us now assume that compartment 1 contains $N_{01} = 10^8$ clonogens with $\alpha_1 = 0.4$ Gy^{-1} and compartment 2

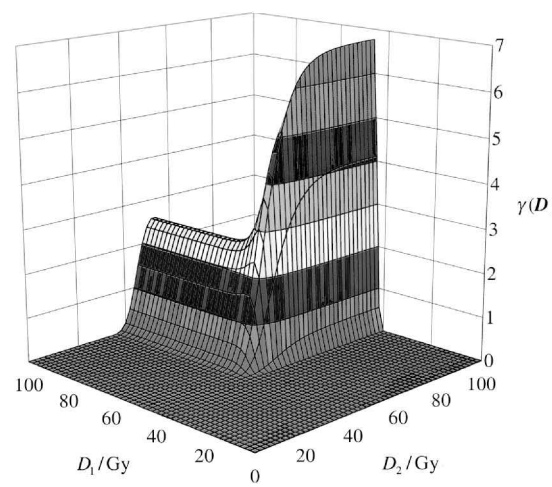


Fig. 1. $\gamma(D)$ for a tumor consisting of two compartments with different dose delivery, D_1 and D_2.

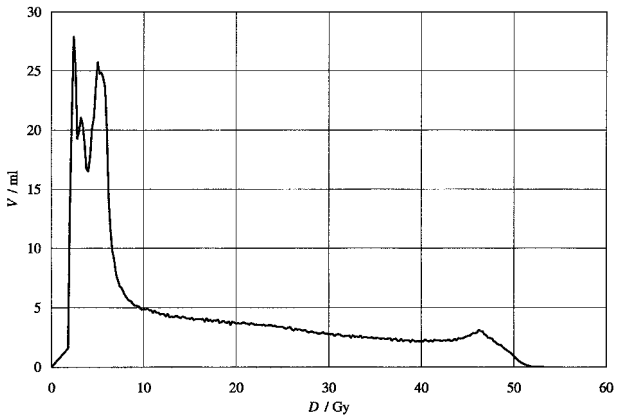


Fig. 2. A typical dose-volume histogram for the lung when treating the chest wall in cancer mammae using parallel opposed beams.

$N_{02} = 1000$ clonogens with $\alpha_2 = 0.13$ Gy^{-1}. In Fig. 1, $\gamma(\boldsymbol{D})$ according to equation [40] can be seen to deviate considerably from the values given by homogeneous dose distributions where $\gamma \approx 3$. The highest γ is almost the same as γ for the compartment with 10^8 clonogens.

Lung response to non-uniform dose distributions

A typical dose-volume histogram (DVH) for the lung when treating breast cancer with tangential fields to 50 Gy is shown in Fig. 2.

Applying the relative seriality model (22) with parameters $D_{50} = 22$ Gy, $\gamma = 2$, and $s = 0.01$, the probability of injury to the lung becomes 7%. Assume now that the dose to the target is raised to 52 Gy instead of 50 Gy, i.e. a 4% increase of dose. How much will this affect the complication probability? Using equation [11] on the DVH in Fig. 2, we find that $\gamma(\boldsymbol{D}) \approx 0.79$ for this particular dose distribution. An increase in the dose distribution by 4% will thus increase the probability of lung complications by $0.8 \times 4 \approx 3\%$. The approximate expression [37] gives in this case an increase by $1.0 \times 4 = 4\%$, and the more accurate expression [34] gives $0.83 \times 4 \approx 3\%$.

Sensitivity analysis of treatment plans

When modern tools for treatment plan optimizations are used, with objectives based on either physical (dose distribution) or radiobiological models, there is still need for analysis of the final result in terms of robustness. This section briefly describes how the present definition of the normalized dose-response gradient can be of use in this context.

In Fig. 3 we show a radiobiologically optimized 5-field 50 MV prostate treatment, where the objective was to maximize the probability of complication-free tumor control P_+ (22). The radiobiological parameters used are listed in Table 1.

Table 1

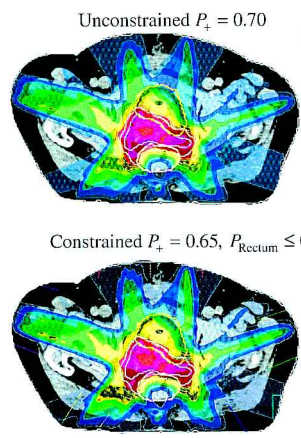
Radiobiological data usesd in Fig. 3

Tissue	D_{50}/Gy	γ	s	Endpoints
Rectum	80	2.2	0.7	Proctitis, necrosis, stenosis
Bladder	80	3.0	0.2	Contracture, volume loss
Surrounding	60	2.0	1.0	
Gross tumor	78	4.5	–	Control
ITV	78	4.5	–	Control

Since this is an unconstrained P_+ optimization, the normalized dose-response gradients are $\gamma_B = \gamma_I = 2.1$. The normalized dose-reponse gradient for the rectum, $\gamma_{Rectum} = 0.62$, implies that a 5% change in dose will change the rectal complications by 3.1%. In the lower panel of Fig. 3 the objective function is still the probability of complication-free tumor control, but now with the additional constraint that the probability of severe injury of the rectum should be less than 1%. This gives a normalized dose-response gradient for the rectum of $\gamma_{Rectum} = 0.19$, so that, for example, a 5% change in dose will only change the rectal complications by less that 1%. The fact that the optimization is constrained is also reflected in the fact that $\gamma_B \neq \gamma_I$.

CONCLUSIONS

The presently defined generalized dose-response relation gradient is a very useful concept for use with the heterogeneous dose delivery that is becoming increasingly common in modern radiotherapy. The definition and use of this new concept in a number of clinically important cases are demonstrated, indicating the importance of being able to quantify also the dose-response gradient with strongly heterogeneous dose delivery. In order to quantify the changes in response as a function of a change from a



Tissue	P_U	γ_U	P_C	γ_C
Bladder	0.039	0.073	0.034	0.064
Tumor	0.87	2.1	0.78	3.1
Rectum	0.051	0.62	0.01	0.19
Stroma	0.17	2.1	0.13	1.6

Fig. 3. Upper panel: A 5-field prostate treatment plan optimized with unconstraine P_+ maximization. Lower panel: The same case, but with the constraint that less than 1% probability of injury to the rectum should be allowed.

non-uniform dose distribution, this new concept is very useful, not least during radiobiological treatment optimization.

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