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MODELING OF NORMAL TISSUE RESPONSE TO RADIATION: THE CRITICAL VOLUME MODEL

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Purpose: A model for calculating normal tissue complication probability in response to therapeutic doses of radiation is presented.

Methods and Materials: The model which we call the "critical volume model" is based on a concept of functional subunits defined either structurally (e.g., nephrons) or functionally, and an assumption that normal tissue complication probability is fully determined by the number or fraction of surviving functional subunits composing an organ or tissue. The essential features of the model are that it takes into account variations in tissue radiosensitivity and architecture of an organ for a single patient and for a patient population, and predicts the normal tissue complication probability under conditions of 3-dimensional inhomogeneity of the dose distribution. The model can be used for Integral Response, or "parallel," organs (where all functional subunits are performing the same function in parallel and the output of the organ is the sum of the outputs of the functional subunits and for Critical Element, or "serial," organs (where damage to one functional subunit results in an expression of damage for the whole organ). The model combines into one compact scheme new concepts and several ideas and models which have been previously developed by other investigators.

Results: The behavior of the model is presented and discussed for the example of the kidney, with clinical nephritis as the functional endpoint.

Conclusions: The model has the potential to be a useful tool for evaluation and optimization of 3-dimensional treatment plans for a variety of types of normal tissues.

Modeling, Normal tissue, Complication probability, Normal tissue complication probability, Dose-response, Treatment planning.

INTRODUCTION

The optimization and quantitative evaluation of 3-dimensional (3-D) radiotherapy plans require not only a knowledgeable planner and a computer powerful enough to be able to calculate 3-D dose distributions in a reasonable time, but also tools that make quantitative evaluation possible, reliable, and clinically sound. One such tool is the modeling of the influence of fractionated radiotherapy on the biological response of normal tissues.

Many ingenious experiments investigating the influence of dose and fractionation schemes on the radiobiological response of various tissues have been performed. A variety of mathematical models have been proposed to describe the shape of the dose-response curves obtained from these experiments. Longstanding clinical experience and limited experiments have provided clinical data (of various quality) over the years (3, 5). For all that, not much has been proposed for modeling normal tissue complication probabilities (NTCP) under realistic conditions where an inevitably inhomogeneous dose distribution is delivered during fractionated radiotherapy (7, 11, 13, 14, 17, 22, 28–30).

As we mentioned elsewhere (17, 19) for optimization and plan evaluation purposes, it may not be crucial to calculate complication probabilities with high accuracy. It is sufficient when these models correctly describe the behavior of complication probabilities as a function of the various parameters of the treatment plan: physical (dose), geometrical (volume and tissue architecture), radiobiological (tissue sensitivity), and temporal (dose fractionation). The rationale for developing models based on radiobiological principles is to allow the evaluation and scoring of treatment plans in a more quantitative and clinically coherent manner that reflects what is known, or is likely, from clinical experience and laboratory experiments. More institutions will soon be using 3-D treatment planning with 3-D data regarding a patient's anat-

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omy and the delivered dose distribution, and more treatment machines will soon be capable of delivering advantageous but more complex dose distributions. For these reasons, it is likely that there will be an increasing demand for the objective evaluation of competing treatment plans and for computer optimization of the dose distribution. To satisfy these expectations we need models that can quantitatively describe the radiobiological response of various tissues and organs.

The aim of this investigation was to develop a model which allows calculation of NTCP for functional end-points, and takes into account three intrinsic aspects of radiotherapy: spatial heterogeneity of the dose distribution, variable sensitivity of the irradiated tissues (both intra-variability within a patient and inter-variability among patients), and fractionation of dose. The model is proposed as a tool for quantitative plan evaluation and computer optimization of 3-D treatment plans.

METHODS AND MATERIALS

It is assumed that the effect of radiation at the cellular level is entirely determined by the fraction of surviving cells. In other words, cellular isoeffects correspond to the same number (or fraction) of surviving cells. It has been proposed and then experimentally supported that cellular radiation effects (E) (such as, for example, chromosome aberrations or cell reproductive death) as a function of dose d can be well approximated by a quadratic function (1):

$$E(d) = \alpha d + \beta d^2, \qquad \text{(Eq. 1)}$$

where α and β are empirical parameters. In fractionated radiotherapy, a total dose D is delivered in n fractions (not necessarily of equal dose d) and equation (1) becomes:

$$E(D) = \sum_{i=1}^{n} \alpha d_i + \beta d_i^2 \qquad \text{(Eq. 2)}$$

where

$$D = \sum_{i=1}^{n} d_i.$$

A time factor to account for repair can be added to Equation (1) and the influence of repopulation can also be readily included in this model. The surviving fraction of cells (or the probability of survival of each cell) can be calculated assuming stochastic killing of cells and Binomial statistics—that is, S(D) is the probability that the event characterized by the frequency distribution E(D) will not occur:

$$S(D) \cong \exp(-E(D)). \qquad \text{(Eq. 3)}$$

For the purpose of modeling radiation-response, a tissue can be described as being composed of functional subunits (FSU's) defined either structurally—for example nephrons in the kidney composed of renal tubule cells, acini in the lung composed of alveoli, intestinal crypts in the intestine, lobules in the liver, or functionally—as the maximum volume/area that can be repopulated by one clonogenic cell (28). It has also been proposed (28) that the radiobiological response of a particular organ is governed by: the number of cells per FSU, the radiosensitivity of those cells, the number of FSU's, the architecture of the tissue ("parallel" or "serial"), and the relationship between the number of surviving FSU's and the probability of complication for a given end-point.

Assuming that an FSU is capable of regenerating from one clonogenic cell (this assumption was examined, for example, for the kidney by Withers et al. (27)) the probability of killing one FSU can be expressed as follows:

$$P_{FSU} = (1 - S)^k = (1 - \exp[-\sum_{i=1}^{n} (\alpha d_i + \beta d_i^2)])^k \qquad \text{(Eq. 4)}$$

where k is the number of cells per FSU.

Let us next assume that the organ consists of N such FSU's and that the organ loses its normal functionality when more than M FSU's are depleted (we also define μ = M/N). For example, normal renal function can be maintained with about 30% to 50% of healthy nephrons (which can be associated with FSU's) (6, 25). When uremic death is the end-point, the complication occurs when the number of killed nephrons exceeds approximately 90% of the total number of nephrons (6, 9). The probability that t of the N FSU's is killed is given by:

$$P_t = \binom{N}{t} P_{FSU}^t (1 - P_{FSU})^{N-t}$$

where $\binom{N}{t}$ is the binomial coefficient. The probability that more than M of the N FSU's is killed is then given by:

$$P = \sum_{t=M+1}^{N} P_t = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^t (1 - P_{FSU})^{N-t}. \qquad \text{(Eq. 5)}$$

The above expression is known as the cumulative binomial probability (20).

In the case of the kidney, the total number of nephrons N is about 10^7 (assuming that the total number of cells per kidney [the product Nk] is 10^{11} and that nephrons contain about k = 10^4 cells) (27). The number of surviving FSU's necessary to maintain function in the organ M is typically of the order of, or an order of magnitude less than, the total number of FSU's, N. For such values of

N and M the binomial distribution of Equation (5) can be well approximated by the normal distribution (10)*:

$$P = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^{t}(1 - P_{FSU})^{N-t}$$

$$\approx \frac{1}{\sigma_{FSU}\sqrt{2\pi}} \int_{-\infty}^{M} \exp\left(-\frac{(x - NP_{FSU})^2}{2\sigma_{FSU}^2}\right) dx \quad \text{(Eq. 6)}$$

where

$$\sigma_{FSU} = \sqrt{NP_{FSU}(1 - P_{FSU})}.$$

For tissues having the so-called critical element or serial architecture (28)—that is, for organs that survive only when all FSU's survive (the spinal cord is thought to be such an organ), one has the special case of M = 0. Equation (5) then reduces to:

$$P(M = 0) = \sum_{t=1}^{N} \binom{N}{t} P_{FSU}^{t}(1 - P_{FSU})^{N-t}$$

$$= 1 - P_0 = 1 - \binom{N}{0} P_{FSU}^{0}(1 - P_{FSU})^{N}$$

$$= 1 - (1 - P_{FSU})^{N}. \quad \text{(Eq. 7)}$$

Equation (7) is the familiar expression for the critical element tissue architecture that was developed by Schultheiss (22) and which we analyzed elsewhere (17).

Another special case is when M = N − 1 that is, when the organ survives if at least one FSU survives. This is the case for tumors where the usual assumption is that local control is achieved when all clonogenic cells are destroyed. In this case, expression (5) reduces to:

$$P(M = N - 1) = P_{FSU}^{N} = (1 - S)^{kN} \quad \text{or}$$

$$\log P = kN \log(1 - S).$$

The product kN is the total number of tumor cells and is proportional to the tumor volume. Modeling of tumor response is beyond the scope of this paper and will not be further discussed here; however this model can clearly accommodate estimation of TCP.

Inhomogeneity of dose distribution

Under the assumption that the complication probability is a function of the number of surviving FSU's, the extension of our model to the case of an inhomogeneously irradiated organ is straightforward. Let us assume that an irradiated organ can be partitioned into R near-homogeneously irradiated sub-volumes (for example, represented by bins of a differential dose-volume histogram) each of which contains L_i FSU's and receives a dose D_i. The total number of killed FSU's, N_{FSU}^{killed}, is equal to the sum of killed FSU's within each of the sub-volumes:

$$N_{FSU}^{killed} = \sum_{i=1}^{R} L_i P_{FSU}^{i}(D_i) \quad \text{(Eq. 8)}$$

where

$$\sum_{i=1}^{R} L_i = N.$$

The effective probability of killing one FSU, P_{FSU}, is then expressed as follows:

$$P_{FSU}^{eff} = \frac{N_{FSU}^{killed}}{N} = \frac{\sum_{i=1}^{R} L_i P_{FSU}^{i}(D_i)}{N} = \sum_{i=1}^{R} \nu_i P_{FSU}^{i}(D_i) \quad \text{(Eq. 9)}$$

where ν_i is a partial volume corresponding to the i'th homogeneously irradiated sub-volume.

It is worth noticing that it is not necessary to count FSU's in sub-volumes or to calculate the partial volumes ν_i. The effective complication probability for one FSU, P_{FSU}^{eff}, can be calculated using a point-based approach (when points are homogeneously distributed inside the volume of interest—not necessarily on a regular grid (16)) that is:

$$P_{FSU}^{eff} = \frac{1}{N_P} \sum_{i=1}^{N_P} P_{FSU}^{i}(D_i) \quad \text{(Eq. 10)}$$

where N_P is the number of calculational points inside the organ of interest.

P_{FSU}^{i} in Equations (9) or (10) can be calculated using equations (2–4). The NTCP for the entire, inhomogeneously irradiated organ can then be calculated using Equation (5) or Equations (6) or (7)—with P_{FSU} in Equation (5) replaced by P_{FSU}^{eff} from Equation (10).

Heterogeneity of the model parameters

Equations (5–10) assume perfect homogeneity of the irradiated tissues, that is, no variation of the parameters

* Lyman (11) proposed a phenomenological model for NTCP using the normal distribution:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2}\, dx \quad \text{where} \quad t = \frac{D - D_{50}}{aD_{50}}.$$

Where a is a parameter which governs the slope of the function, obtained from fitting a clinical data, v is a partial volume and D_{50} is a dose leading to complications in 50% of cases.

Expression (6) of our model can be written in a similar form:

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2}\, dx \quad \text{where} \quad t = \frac{M - NP_{FSU}}{\sigma_{FSU}}.$$

Correspondence of Lyman's phenomenological parameters and ours will not be discussed further in this paper.

of the model (α, β, k, M, and N). However, it is quite obvious (and experimentally documented) that cells, even within the same organ, differ in radiosensitivity, that not every nephron contains exactly 10^4 cells, that not every kidney loses its functionality when exactly 30% (for example) of its nephrons are killed, etc. There are two types of heterogeneity: heterogeneity influencing the radiobiological response of a particular patient; and heterogeneity influencing the outcome for a patient population. It is important to emphasize that observed dose response curves are, by definition, expected values for a patient population and, as such, do not describe the response of any one patient.

In our model, heterogeneity of tissues is taken into account assuming a normal (or log-normal in the case of k) distribution of the model parameters—with no correlation between parameters (i.e., univariate distributions are used). Although both assumptions can be questioned, they represent a reasonable approach. The influence of the dose uncertainty on the dose-response curves can be modeled by a simple and obvious extension of the model, but is not analyzed here.

NTCP for an individual

Statistically, the effective probability of killing one FSU for an individual can be considered equal to the expected value of the probability of killing one FSU expressed in Equation (4) weighted by the normal probability density function G_X which expresses intra-patient heterogeneity:

$$\bar{P}_{FSU} = \int G_x^{ind} P_{FSU}\, d\vec{x}^{ind}, \qquad \text{(Eq. 11)}$$

where P_{FSU} is the probability that a perfectly homogeneous FSU loses its normal functionality (Eq. 4) and the probability density function G_X is the product over all parameters of the model which vary for an individual, that is, α, β and the size of the FSU expressed by k. A normal distribution is used for the parameters α, β, and a log-normal distribution is used for the parameter k (i.e., from now on the number of cells per FSU, k, is replaced by K = log(k)):

$$G_x^{ind} = \frac{1}{(\sqrt{2\pi})^3 \sigma_x^{ind}} \times e^{-[(\alpha-\bar{\alpha})^2/2\sigma_\alpha^2 + (\beta-\bar{\beta})^2/2\sigma_\beta^2 + (K-\bar{K})^2/2\sigma_K^2]} \qquad \text{(Eq. 11a)}$$

$$\sigma_x^{ind} = \sigma_\alpha \sigma_\beta \sigma_K$$

and the integral of equation (11) is 3-dimensional:

$$d\vec{x}^{ind} = d\alpha d\beta dK.$$

The $NTCP^{ind}$ for an individual is then calculated using Equation (5).

Individual response vs. response of population

As already mentioned, the observed response curves are per se a measure of the response of a patient population. Mathematically, the observed response curve can be expressed as the integral of the individual response-curve with the probability density function describing the spectrum of possible values of the parameters of the individual response curve over the patient population:

$$NTCP^{pop} = \int G_y^{pop} NTCP^{ind}\, d\vec{y}^{pop} \qquad \text{(Eq. 12)}$$

where

$$G_y^{pop} = \frac{1}{(\sqrt{2\pi})^5 \sigma_y^{pop}} \times e^{-[(\bar{\alpha}-\bar{\bar{\alpha}})^2/2\sigma_{\bar{\alpha}}^2 + (\bar{\beta}-\bar{\bar{\beta}})^2/2\sigma_{\bar{\beta}}^2 + (\bar{K}-\bar{\bar{K}})^2/2\sigma_{\bar{K}}^2 + (\bar{M}-\bar{\bar{M}})^2/2\sigma_{\bar{M}}^2 + (\bar{N}-\bar{\bar{N}})^2/2\sigma_{\bar{N}}^2]},$$

$$\sigma_y^{pop} = \sigma_{\bar{\alpha}} \sigma_{\bar{\beta}} \sigma_{\bar{K}} \sigma_{\bar{M}} \sigma_{\bar{N}},$$

$$d\vec{y}^{pop} = d\bar{\alpha} d\bar{\beta} d\bar{K} d\bar{M} d\bar{N}.$$

It should be emphasized that the distributions of the parameters α, β, and K for the internal integral ($NTCP^{ind}$) are around values $\bar{\alpha}$, $\bar{\beta}$, and $\bar{K}$ which are variables of the external integral ($NTCP^{pop}$).

The model expressed in Equation (12) is an 8-dimensional integral. It is very time-consuming to evaluate (see notes on the computer implementation of the model in the Appendix). More importantly, it has more parameters than the available data can probably differentiate. For these reasons, and because we assumed a normal probability density function G_x for all the model parameters with no correlation between them, it is reasonable to simplify the integral by assuming that the heterogeneity of all parameters can be expressed by only two parameters (one for the individual response and one for that of the population). For example, one can vary only the parameter K (representing the logarithm of the number of cells per FSU) for an individual and the parameter M (or μ) (the number [or the ratio] of FSU's necessary to maintain organ function) with coefficients of variation σ^{ind} and σ^{pop} being dummy parameters obtained from fitting the model to experimental and/or clinical data. Equation (12) can then be simplified to the 2-dimensional integral, much easier to evaluate:

$$\left.\begin{aligned} NTCP^{pop} &= \int_{-\infty}^{\infty} G^{pop} NTCP^{ind}\, dK dM \\ G^{pop} &= \frac{1}{(\sqrt{2\pi})\sigma^{pop}} e^{-[(\bar{M}-\bar{\bar{M}})^2/2(\sigma^{pop})^2]} \\ G^{ind} &= \frac{1}{(\sqrt{2\pi})\sigma^{ind}} e^{-[(K-\bar{K})^2/2(\sigma^{ind})^2]}. \end{aligned}\right\} \qquad \text{(Eq. 13)}$$

For the special case of critical element architecture for which M = 0 (and there can therefore be no variation of M), a variable other than M needs to be used as the integrated variable in the simplified model. We have varied the parameter K for both the individual and the population with good results; the simplified model is flexible enough to fit the available clinical data with acceptable accuracy.

It should be emphasized that the above approximations do not shortchange the model of NTCP (Eq. 5-6) as a function of the model parameters α, β, K, M, N, and D. It only simplifies the way the *distributions* of these parameters are taken into account.

RESULTS

To illustrate the usefulness of our proposed critical volume model, we present calculations of the probability for a late complication of the kidney (severe clinical nephritis, grade 3/4 according to the RTOG/EORTC classification) as an end-point. It was assumed that on average a normal kidney contains 10^{11} tubule epithelial cells and that there are 10^7 nephrons each containing 10^4 cells (27). α and β were given values of 0.15 Gy^{-1} and 0.09 Gy^{-2}, respectively. These values are estimates rather than clinically proven numbers (23, 25). The α/β ratio of 1.7 Gy is, however, consistent with the (sparse) data obtained for late functional end-points (23, 24). We assumed that severe clinical nephritis occurs when the number of functioning nephrons falls, on average, below 30% of the total number of nephrons in one kidney (6, 25, 30). We also assumed that, instead of using absolute numbers for parameters N (the total number of FSU's) and M (the number of FSU's that can be destroyed and still not lose kidney function), we can use the normalized value, μ, that is, the ratio M/N (which reduces by one the dimensionality of the integral in expression (12)).

Unless explicitly specified, all calculations were performed using the full model (Eq. 12 with the parameter μ replacing the parameters N and M), with the coefficients of variation of all model parameters equal to 15% (a reasonable estimate based on our experience with the model) and assuming a dose per fraction of 2 Gy.

Figure 1 shows the NTCP as a function of the total dose for various sizes of the critical volume that is, for various proportions of FSU's which can be depleted without disrupting the normal functioning of the organ. For comparison, the solid line represents the probability of killing one FSU (parameters α and β and the number of cells per FSU, k, were varied). The open squares are the results for a critical element (CE) type of normal tissue (Eq. 7) assuming that the organ consists of 100 critical elements (FSU's). The dose-response relationship for that CE organ closely follows the dose-response relationship for the integral response organ under assumption that destroying 1% of the volume causes the complication (for example, destroying 1% of the volume of spinal cord results in myelopathy). For the CE calculations M is equal to zero and there is no variation in M between patients.

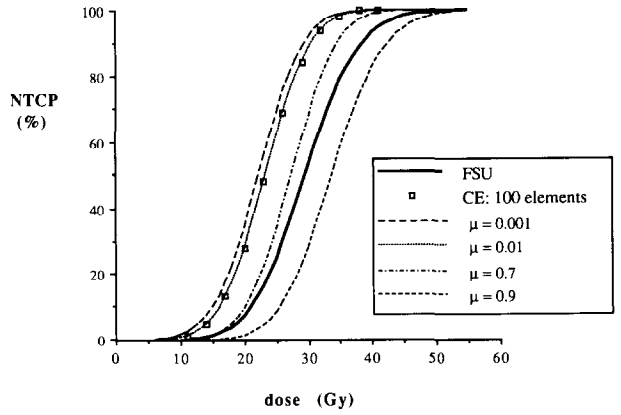

Fig. 1. Dose-response curves for a single functional subunit (solid line) and for the whole organ for one individual for various sizes of the critical volume (defined by the parameter M). Open squares represent results for a critical element organ with 100 critical elements.

The influence of the size of the critical volume (represented by the normalized model parameter μ = M/N) and the size of an FSU (i.e., the number of cells per FSU—the parameter k) on the NTCP are shown in Figures 2 and 3, respectively, for a total dose of 25 Gy.

Figure 4 shows the influence of the number of cells per FSU (represented by the model parameter k). As k increases, the dose-response curves shift towards higher doses and flatten out. The solid line represents calculations for 10,000 cells per FSU, which is the value taken for modeling nephron and kidney response. Because we assumed that the coefficient of variation of all model parameters is 15% and that k is log-normally distributed, when the mean number of cells per nephron is 10,000, 95% of nephrons contain between 5,000 and 20,000 cells.

According to the proposed model, the probability of failure of an organ depends upon the fraction of surviving FSU's and is not a function of the fraction of surviving cells. For example, irradiating the whole organ to a certain dose level may kill more cells but less FSU's than when the same organ is only partially irradiated (i.e., with part of the organ receiving negligible dose), but to a higher dose, depleting practically all irradiated FSU's. This is because of the assumption that an FSU is capable of regenerating from one clonogenic cell and that there is no functional difference between unirradiated and surviving FSU's. This effect suggests that, at least for organs that can be described by our model, spreading a lower dose over the entire organ might be more beneficial than partial irradiation to a higher dose. The eventual gain depends on the dose-volume effect for the particular organ. Because most organs exhibit volume effects, the importance of modeling the effect of inhomogeneous dose distributions becomes apparent.

Figure 5 shows the NTCP as a function of the average percentage of destroyed FSU's for various critical volumes.

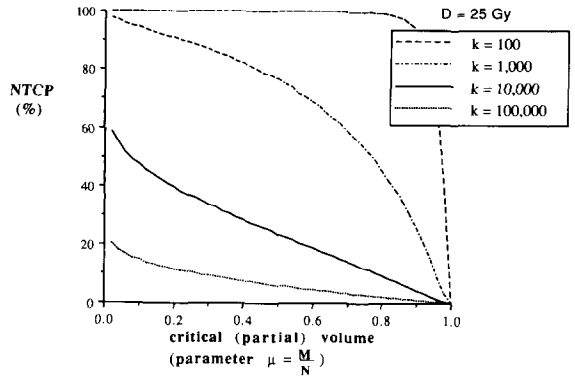

Fig. 2. Sensitivity of normal tissue complication probability to the size of the critical volume for four sizes of the functional subunit for a uniform dose of 25 Gy.

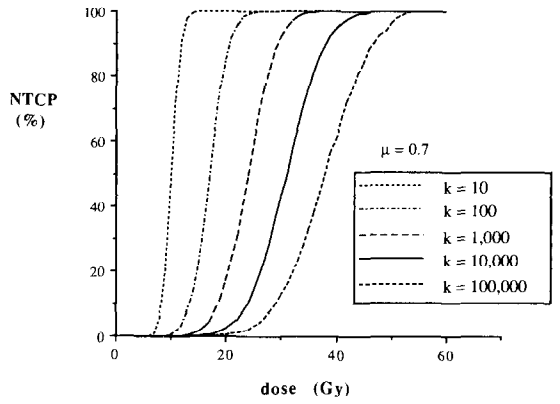

Fig. 4. Dose-response curves for various sizes of the functional subunit (i.e., various numbers of cells per FSU).

The average percentage of destroyed FSU's is also equal to the mean probability of destroying a single FSU—and also represents the fractional volume of the organ which is destroyed. In our model, this relationship is derived from the basic parameters of the model but, it could be equally specified by a radiotherapist based on his or her judgement of the importance of partial inactivation of functional subunits. The percentage of destroyed FSU's is itself a sigmoidal function of dose (see solid line in Fig. 1). The relationship shown in Figure 5 should not be confused with the dependence of NTCP on the partial volume irradiation which is discussed below.

Figures 6a and 6b show the influence of the linear-quadratic model parameters α and β on the NTCP. Figure 6a shows the NTCP as a function of the parameter α for three values of the parameter β. Figure 6b presents the NTCP as a function of α/β ratio. In both figures the NTCP was calculated for a dose of 25 Gy.

Figure 7 shows the NTCP for a patient population as a function of the dose delivered in 2 Gy fractions for five levels of inhomogeneity of the model parameters. The parameters α, β, and M are normally distributed and the parameter k is log-normally distributed (i.e., K = log(k) is normally distributed) with equal standard deviations of 5, 10, 20, 30, and 40%. The dose response curves have a slope factor γ_{50} (defined as $D(\partial NTCP/\partial D)$ at the 50% complication level (8)) of 9.0, 4.4, 2.1, 1.5, and 1.1, respectively. Note that the variation of the model parameters changes only the slope of the dose-response curve. The position of the curve at the 50% complication level (31 Gy) is fully determined by the mean values of the model parameters.

The NTCP for a patient population (and only such data can be experimentally observed) is shown in Figure 8 and compared with the NTCP calculated for an individual. The standard deviations of all parameters for an individual and for the patient population are assumed to be equal to 0.15. The resultant γ_{50} slope factor for the individual is 4.8 and for the population is 2.2; the latter value is in good agreement with published data for the kidney (3, 5).

It should be emphasized that the position and slope of the dose-response curves (and as a consequence the tolerance of an organ) significantly depend on the fraction-

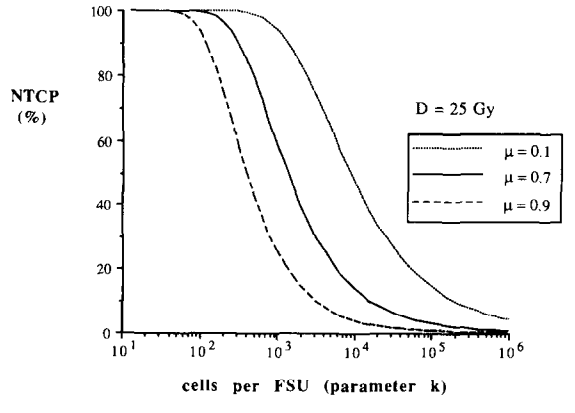

Fig. 3. Normal tissue complication probability as a function of the size of functional subunit for three sizes of the critical volume and for a uniform dose of 25 Gy.

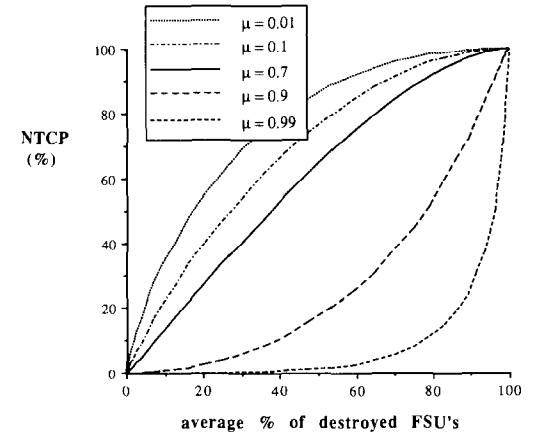

Fig. 5. Complication probability for the organ as a function of the complication probability for a single functional subunit (or the average percentage of destroyed FSU's) for various sizes of the critical volume.

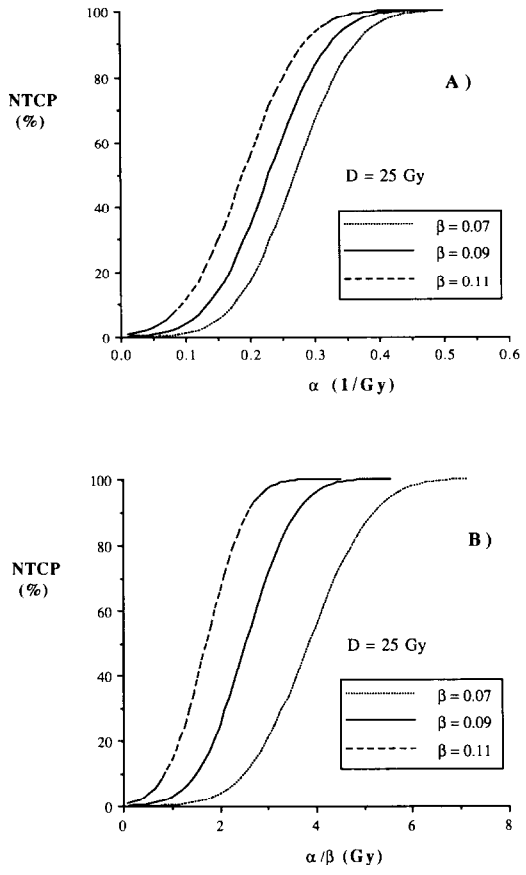

Fig. 6. (A) Sensitivity of normal tissue complication probability to parameter α for three values of parameter β of the linear-quadratic model. (B) Normal tissue complication probability as a function of the α/β ratio.

ation scheme. Figure 9 shows two dose-response curves for two fractionation approaches. The solid line represents the NTCP as a function of dose when the dose is delivered in equal fractions of 2 Gy each (so the number of fractions is varied); the dashed line corresponds to irradiation with 30 fractions (so the dose per fraction is varied). The im-

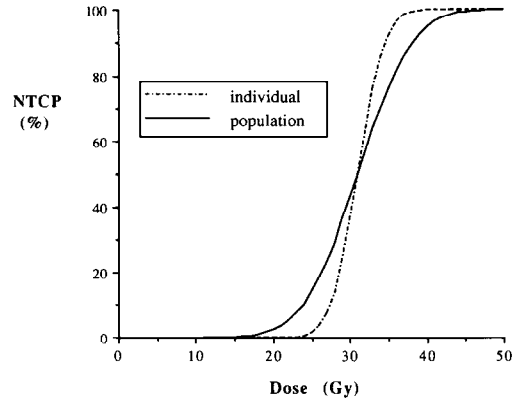

Fig. 8. Complication probability for an individual and for a population assuming a variability of 15% for all parameters of the individual and for the population.

portance of fractionation on the radiobiological response of an organ is further emphasized in Figure 11 below.

The volume dependence of NTCP for an individual and for a patient population is shown in Figure 10a. In this figure it is assumed that a fraction of an organ receives a dose of 31 Gy (corresponding to 50% complication probability when the whole kidney is irradiated) and the reminder receives essentially no dose. There is a steep increase in NTCP as the irradiated volume exceeds the assumed critical volume of 70% of the total volume. While the NTCP is zero for an individual when the irradiated volume is smaller than the critical volume, it is not so for the patient population. The inhomogeneity of the model parameters (that is, σ's of their normal distributions) was taken to be 10% for an individual and 15% for the patient population. These numbers are our estimates derived from hand-fitting of the available data (3, 5).

The difference between the volume dependence for an integral response organ (with μ = M/N equals 0.7) and a critical element organ (M = 0; equation 7) is shown in Figure 10b. For both models the same values of param-

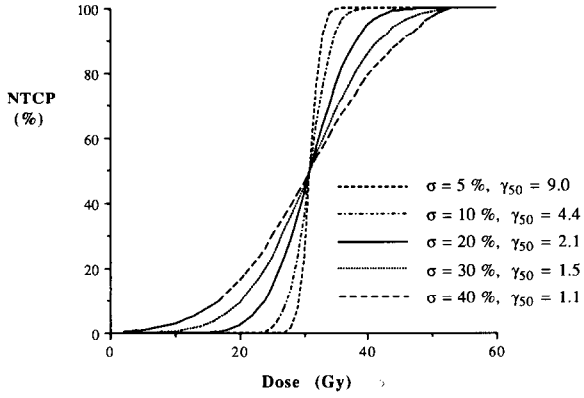

Fig. 7. Complication probability as a function of dose delivered in equal fractions of 2 Gy for five levels of variability of the model parameters represented by equal standard deviations of 5, 10, 20, 30, and 40% of each of the 8 parameters of the model.

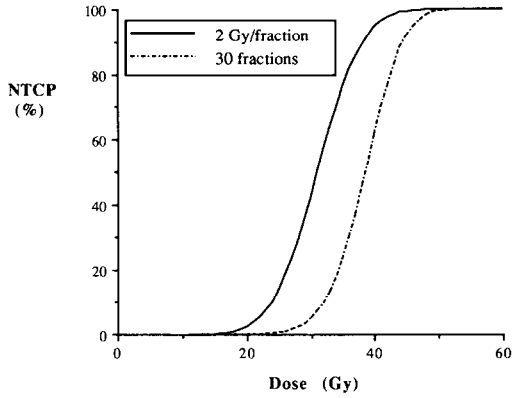

Fig. 9. Complication probability for uniform irradiation according to two fractionation schemes—for constant fractionation doses of 2 Gy (solid line) and for a constant number (30) of fractions (dot-dashed line).

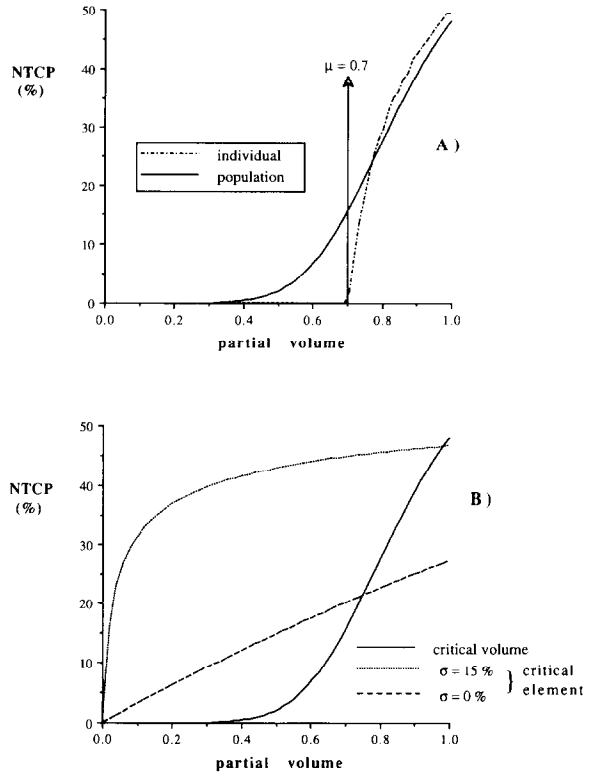

Fig. 10. (A) Complication probability as a function of irradiated partial volume for an individual and for a population for doses resulting in a 50% complication rate for an individual. (B) Comparison of the volume dependence for the critical volume and critical element models with and without taking into account variability of the model parameters.

eters α, β and k were used while the doses were 23 Gy and 31 Gy for the critical element and the critical volume models, respectively (the smaller dose used for the critical element model was designed to achieve a comparable [for a volume of 1.0] NTCP to that for the critical volume model). The fundamental difference between these two tissue architectures (17) is that, at small NTCP's, the critical element model exhibits a linear increase of NTCP with volume irradiated whereas the integral response architecture shows a threshold behavior with a supra-linear response at volumes above the threshold. The greater the variation of the model parameters, the steeper the rise of NTCP as a function of irradiated volume.

Figure 11 shows an example of a dose-volume histogram obtained for a patient's kidney when an upper abdominal tumor was irradiated. The NTCP was calculated assuming two fractionation approaches—both of which lead to the same DVH. In the first, a higher dose per fraction was delivered (2 Gy for the hottest part of the kidney) and the entire kidney was excluded from the irradiated volume when the maximum dose to the kidney reached 30 Gy (i.e., after 15 fractions). In the second approach a smaller dose per fraction was assumed to be delivered and the kidney was within the irradiated volume during all 30 fractions. The physical dose distributions for these two situations are identical. The calculated NTCP for the second fractionation regimen (smaller doses per fraction) is 0.3%—which is substantially smaller than the estimated value of 11% if the same dose were delivered using the higher daily doses.

DISCUSSION

According to the proposed critical volume model, the biological response of a normal tissue depends on the sensitivity of stem cells—for example through α and β parameters of the LQ model—and the organization of the organ into functional subunits (FSU)—through the parameter k defining the size of an FSU. The model assumes that survival of an organ or tissue depends solely on the number or fraction of surviving FSU's. An FSU does not have to be structurally defined, but the concept assumes that all FSU's are equally important and that the volume distribution of surviving FSU's is irrelevant (it has been reported for the kidney, however, that for higher doses surviving nephrons tend to form clusters (27)). There is no agreement as to whether vascular damage itself plays an important role in losing functionality of an organ and the influence of blood-vessel integrity is not taken into account in our model (4, 12, 26, 27).

The basic assumptions of the critical volume model are very general and, as was shown in the Methods section, it can be applied to both "parallel" (integral response) and "serial" (critical element) organs (28) (as well as to tumors). According to the model, the only difference between serial and parallel organs is in the numbers of "strains" of which the organ is composed (i.e., one for serial organs [such as spinal cord] and many for parallel organs [such as kidney]). As Figure 1 shows, there is no distinguishable difference in dose-response between a serial organ composed of 100 critical elements (the destruction of any one of which results in expression of the complication) and a parallel organ which does not exhibit any

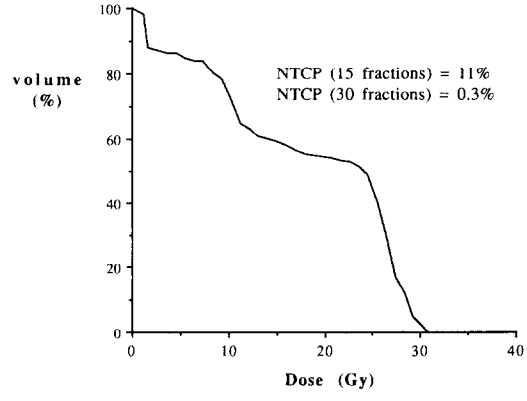

Fig. 11. A clinical example of a dose-volume histogram for a kidney and the corresponding normal tissue complication probabilities calculated for two fractionation approaches (see text).

damage when the proportion of killed FSU's is smaller than 1% (i.e., 1/100 of the total volume [for any total number of FSU's]). This is because of the assumption that all FSU's respond independently and that a complication probability depends upon the fraction of surviving FSU's. However, the two are very clearly distinguished in their NTCP versus volume behavior—as demonstrated in Figure 10.

The size of FSU's is a significant factor influencing the position and the slope of the dose-response curves (Fig. 2–4). Larger FSU's (i.e., FSU's containing more cells) are more radioresistent (have a larger D_{50}) because, according to our assumptions, an FSU can be rescued by a one surviving cell (however, this would also be true if more than one cell were necessary to rebuild an FSU). The apparent flattening of the dose-response curves in Figure 4 caused by variation of D_{50}. The γ_{50}, which is the measure of the relative steepness of the dose-response curves, is constant for all sizes of FSU. The γ_{50} is primarily governed by the level of inhomogeneity of the model parameters as is shown in Figure 7.

The variation of NTCP for the kidney as a function of volume under conditions of partial volume irradiation (Fig. 10a) has a similar shape to that obtained, for example, by fitting clinical data by Burman *et al.* (3) for the liver (Burman *et al.* do not show graphically volume dependence for the kidney). The liver can be also considered a critical volume organ. The volume dependence for critical element organs (Fig. 10b) has a different behavior from that of critical volume organs; the NTCP as a function of irradiated volume rises linearly and then flattens out. A similar shape was obtained by Burman *et al.* for the esophagus which some consider to have a serial architecture. The substantial difference between the volume dependence of NTCP for integral response organs and critical element organs underlines the importance of properly modeling volume effects when NTCP is calculated for inhomogeneous dose distributions.

The model intrinsically takes into account fractionation effects and clearly shows that the response (tolerance) of an organ can depend substantially on the fractionation scheme. As Figures 9 and 11 show, the predicted response of an irradiated kidney to a specific dose distribution depends on the way the dose was delivered. When the kidney is irradiated with higher daily doses and then excluded from the irradiated volume the NTCP is predicted to be larger (by almost two orders of magnitude) than when the kidney is within the irradiated volume during all fractions and so receives smaller daily doses. This considerable effect (which yet has to be quantitatively confirmed in clinical trials) suggests caution while evaluating competing plans based on DVH's and derived complication probabilities which do not take into account fractionation effects (15, 31). We address the problem of biologically normalized DVH's (BNDVH's) elsewhere (18) by resolving the dose at each calculational point from each field into a biologically equivalent dose when delivered in equal fractions of 2 Gy each. The NTCP model presented in this paper is compatible with the BNDVH concept.

The essential characteristic of the model is that it takes into account variations in radiosensitivity and tissue architecture within an irradiated organ and between patients. These variations have been modeled in a mathematical manner similar to that used by Goitein (8) to model tumor control probability and by Boyer & Schultheiss (2) and Zagars *et al.* (32) to model effects of dosimetric and clinical uncertainties on complication-free tumor control.

Although this paper uses as an example a situation involving a late tissue response, a time factor to account for repair can easily be included in Equations (1) and (2) of the model and acute responses for tissues whose cells turn over quickly can be also modeled. The particular model describing the cell surviving fraction is not essential to our model; the NTCP can be calculated and analyzed starting with Equation (4) and using, instead of the linear-quadratic model, any other cell-survival model—or, indeed, measured data for surviving fraction as a function of dose per fraction.

Unlike the problem of controlling a tumor, in which it is thought that *all* clonogenic tumor cells have to be destroyed, normal tissues or organs may maintain their functionality when at least a certain *number* or *proportion* of FSU's survive. The model presented here can be applied to both situations using the total number of FSU's (the model parameter N) and the number of FSU's needed for maintaining normal functionality, the model parameter M, or the ratio $\mu = M/N$ when the critical volume can be expressed as a fractional volume. In the second case, the response of normal tissue does not depend on the absolute number of cells (for example the overall size of the irradiated organ).

We plan to apply our model to existing data collected by Emami *et al.* (5) and to compare our best fits to these data to results obtained by Burman *et al.* (3) using a phenomenological model developed by Lyman (13).

CONCLUSION

A radiobiological model of normal tissue complication probability (NTCP) which we call the "critical volume model" is presented. It is based on the concept of functional subunits (FSU's) and, in the development presented here, uses the linear-quadratic (LQ) model. It takes into account inhomogeneity of the irradiated tissues, inhomogeneity of the dose distribution and fractionation scheme. Intra- and inter-patient variability of the model parameters (i.e., α and β of the LQ model, the number of FSU's, the number of cells per FSU, and the number or fraction of FSU's necessary to maintain functioning of an organ) are modeled assuming them to follow normal or log-normal distributions. The critical volume model can represent both the critical element architecture (M =

0) and the integral response architecture of Withers *et al.* (28). The model allows one to calculate NTCP for a partially irradiated organ or, in the more general situation, for any inhomogeneous dose distribution and non-standard fractionation scheme. Randomly distributed points within each volume/organ of interest are sufficient for the calculation (16, 17) and NTCP's can be calculated directly from the calculational points without constructing dose-volume histograms. Although the calculation of NTCP using the full model including the individual variation of all model parameters is time consuming, it can be significantly reduced by using the simplified version of the model which assumes that there are only two variable model parameters, one for the patient and the other for the patient population. The model was developed for evaluating and computer optimizing 3D dose distributions. New clinical data regarding the dose and volume dependences of NTCP and their variability among patients, can be easily included in the model by appropriate adjustment of its parameters.

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APPENDIX

Computer implementation of the model

Clinical data regarding complication probability have to be compared with NTCP's calculated for a patient population, using Equation (12). Equation (12) is, however, an 8-dimensional integral which cannot be calculated analytically. Equations (11) and (12) for $NTCP^{ind}$ and $NTCP^{pop}$ are convolution integrals and, theoretically, can be solved using Fast Fourier Transform (FFT) techniques (20). The FFT requires all data to be stored in a matrix. However, zero padding (to overcome the wraparound problem) and eight dimensions make the required matrix too large (at least $16^8 \approx 10^9$ elements) to handle by a microcomputer.

Monte Carlo integration with a smart choice of calculational points, using quasirandom numbers and recursive stratified sampling may be a better approach to solving multidimensional integrals (21). However, solving Equation (12) with reasonable accuracy still required about 10^8 evaluations of the integrated function.

Two orders of magnitude less evaluations were sufficient when the classical Simpson's extended trapezoidal integration formula was used with equally and widely spaced abscissa (20). Our numerical exercises showed that summation within a region of ±3 standard deviations with relatively big steps equal to 1 standard deviation gives an average fractional error smaller than 10% (which is satisfactory for our purposes).

The computational burden can be drastically reduced by using the simplified model expressed in Equation (13). Because in this model there is only one effective coefficient of variation for an individual and one for population, the integral is 2-dimensional and easy to evaluate. Figure 12 shows the γ_{50} slope of the dose-response curve as a function of the coefficient of variation σ for an individual (i.e., assuming that population is homogeneous) and for a population. On this log-log scale the relationship between σ and the γ_{50} is linear which, most likely, is a consequence of the power law relationship between the probability of killing an FSU and the size of the FSU expressed by the parameter k. A standard deviation of 15% applied to all parameters of the full model (Eq. 12) is equivalent (in terms of γ_{50} and all the relationships presented in Figures 1–11) to standard deviations of 20% when the simplified model (Eq. 13) is used.

Another important simplification that can be made for computer implementation of either the full model (Eq. 12) or the simplified model (Eq. 13) is based on the observation that for large numbers of FSU's (say, more than 100) the cumulative binomial probability, or its approximation by the normal distribution (Eq. 6), can be very accurately approximated by a step function:

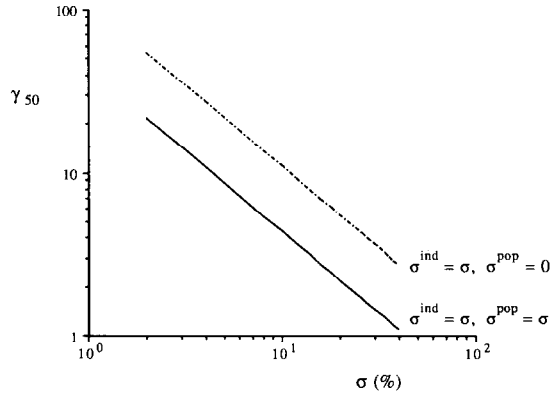

Fig. 12. Slope, γ_{50}, of the dose response curve as a function of heterogeneity of the model parameters for an individual and for a population.

$$P = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^{t}(1 - P_{FSU})^{N-t}$$

$$\approx \frac{1}{\sigma_{FSU}\sqrt{2\pi}} \int_{-\infty}^{M} \exp\left(-\frac{(x - NP_{FSU})^2}{2\sigma_{FSU}^2}\right) dx$$

$$\approx \begin{cases} 1 & \text{for } P_{FSU} \geq \dfrac{M+1}{N+1} \approx \mu \\ 0 & \text{for } P_{FSU} < \dfrac{M+1}{N+1} \approx \mu. \end{cases}$$

Both models have been implemented in FORTRAN on a MicroVax 3200. The calculations can be either point-based or DVH-based. Simpson's Rule (20) is used for integration within a region of ±3 standard deviations for the full model and within a region of ±4 standard deviations for the simplified model. Because the integration intervals, in units of a standard deviation, are always the same (and equal 1 standard deviation for the full model and 0.25 standard deviation for the simplified model) the normal probability function was precalculated at these intervals and tabulated for later table look-up. For 400 calculational points (or bins of a differential DVH) the simplified model calculates NTCP in less than 0.1 sec. The full model is three orders of magnitude slower. Because the simplified model has proven to be a good approximation of the full model, and because there is a lack of clinical data which are needed to take full advantage of the full model, we use the simplified model for routine calculations.