Reporting and analyzing dose distributions: A concept of equivalent uniform dose

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Modern treatment planning systems for three-dimensional treatment planning provide three-dimensionally accurate dose distributions for each individual patient. These data open up new possibilities for more precise reporting and analysis of doses actually delivered to irradiated organs and volumes of interest. A new method of summarizing and reporting inhomogeneous dose distributions is reported here. The concept of equivalent uniform dose (EUD) assumes that any two dose distributions are equivalent if they cause the same radiobiological effect. In this paper the EUD concept for tumors is presented, for which the probability of local control is assumed to be determined by the expected number of surviving clonogens, according to Poisson statistics. The EUD can be calculated directly from the dose calculation points or, from the corresponding dose-volume distributions (histograms). The fraction of clonogens surviving a dose of 2 Gy (SF_2) is chosen to be the primary operational parameter characterizing radiosensitivity of clonogens. The application of the EUD concept is demonstrated on a clinical dataset. The causes of flattening of the observed dose-response curves become apparent since the EUD concept reveals the finer structure of the analyzed group of patients in respect to the irradiated volumes and doses actually received. Extensions of the basic EUD concept to include nonuniform density of clonogens, dose per fraction effects, repopulation of clonogens, and inhomogeneity of patient population are discussed and compared with the basic formula. [S0094-2405(97)00501-4]

Key words: effective uniform dose, EUD, reporting dose, dose-volume distribution, DVH, three-dimensional treatment planning, biological modeling

I. INTRODUCTION

Despite impressive developments in three-dimensional (3-D) treatment planning, until quite recently, the prescription, specification, and reporting of radiation treatments have not received appropriate attention, even in the most advanced radiotherapy centers worldwide.[1–3] For example, a complex three-dimensional target dose distribution is typically reported at a reference point(s),[3] even though modern imaging technologies, fast computers, and advances in 3-D dose calculation algorithms provide accurate knowledge of a patient's anatomy, and a complete 3-D distribution of dose within the irradiated volume. Although cumulative and differential dose-volume distributions/histograms (DVD/DVH) have become indispensable tools for modern 3-D treatment planning,[4,5] their usage for dose specification and reporting is typically limited to selecting a point on a DVD plot to which the prescribed dose is normalized.

On the other hand, because dose is normalized (to a point or to an isodose level), the dose actually delivered depends on the normalization protocol (e.g., the prescribed dose may correspond to a 90% isodose line or to a 95% isodose line). The problem is negligible only when target dose distribution is uniform and, of course, provided that the tolerance of surrounding normal structures allows delivery of the prescribed dose. Unfortunately, dose distributions throughout organs or volumes of interest are never exactly uniform, and may often be far from it, especially for normal tissues. Brahme proposed that, for relatively small dose nonuniformity, the dose effectively delivered to the target can be approximated by the mean target dose.[6] For large dose inhomogeneities Brahme suggests using the minimum target dose. The mean target dose approach assumes that doses above the mean target dose compensate for doses less than the mean target dose. That is, the (unspecified) clinical effect of irradiation is a near-linear function of dose. On the other hand, the minimum target dose approach assumes that a cold spot cannot be compensated by any dose delivered to the rest of the target volume. That is, the dose in excess of the minimum target dose is ignored. Both Brahme's propositions are the first-order approximations that reveal the difficulty and importance of adequate reporting of inhomogeneous dose distributions.

It is quite obvious that an oversimplification is made when the dosimetric aspects of a complex three-dimensional treatment plan are reduced in the patient's records to a dose or a few doses at the reference point or points. Such an oversimplification has an important consequence for statistical analysis of the clinical trials. For example, by assuming that all patients received the same (prescribed) dose, the underlying dose–response relationship is flattened out, and a possible finer structure of the dosimetric data of the trial's arm can be lost. Inadequate dose specification and reporting

seem to be one of the reasons for an ongoing complaint that we do not have ''reliable'' data, or that the data are ''sparse,'' ''uncertain,'' ''of poor quality,'' or ''anecdotal.''

Emerging 3-D conformal radiotherapy techniques and 3-D treatment planning systems provide dose–volume–time-response data that exacerbate the need for more adequate methods of dose specification, reporting, and analysis. The problem has been recognized, but fully satisfying techniques have yet to be developed.[1–3] Some progress is being made. The Nordic countries in Europe have been developing an alternative proposal to the ICRU recommendations.[27] In particular, the Nordic Association of Clinical Physics (NACP) report recommends the arithmetic mean value of the target dose distribution and its standard deviation to be used for dose prescription and reporting.[8] Within the NACP framework Brahme has recently proposed an interesting new formula for the target dose effectively delivered, D_{eff}:

$$D_{\mathrm{eff}}=\overline{D}\cdot\left[1-\frac{\gamma_{50}}{2\cdot P(\overline{D})}\cdot\left(\frac{\sigma}{\overline{D}}\right)^2\right],$$

where $\overline{D}$ is the mean delivered dose, γ_{50} is the slope of the dose–response curve, σ is the standard deviation and $P(D)$ is the probability of local control at the dose D level.

There has also been increasing interest in more quantitative usage of dose-volume histograms for individual patients.[9–18] For example, dose-volume reduction schemes for normal tissues developed by Lyman,[16] and by Kutcher and Burman,[14] have made an important impact on the quantitative evaluation of dose distributions.

It is intuitively logical that, for any inhomogeneous dose distribution delivered to a volume of interest (VOI) according to a certain fractionation scheme, there exists a unique uniform dose distribution delivered in the same number of fractions, over the same total time, which causes the same radiobiological effect. The important feature of this equivalent dose distribution would be its uniformity, which allows one to use a single number to describe the entire VOI dose distribution. Of course, the equivalent dose depends on the considered effect.

Practitioners of radiotherapy know that the clinically relevant effects are not a linear function of dose and irradiated volume, neither for tumors nor for normal organs. Therefore, for the target volume, they intuitively prefer more uniform dose distributions, where the difference between the maximum and the minimum dose is small. In consequence, they minimize the uncertainty in dose ''effectively'' delivered (which, regardless of the considered effect, is always positioned between the maximum and the minimum dose). However, it has been suggested that forcing the target dose distribution to be as uniform as possible, may eliminate some superior but inhomogeneous dose distributions available in a particular case.[19] It has also been shown that computer optimized plans, with or without beam intensity modulation, and with biological objective functions, are often quite inhomogeneous.[9,17,20]

In theory, models of tumor control probability (TCP) and normal tissue complication probability (NTCP) provide a quantitative biophysical measure of a dose distribution.[10–14,16,18,21,22] However, the predictive power of these models have not yet been proven clinically. Although the TCP and NTCP models are potentially very useful, their application without full understanding of the underlying biological mechanisms, the assumptions, and the range of their application, should be discouraged.

There is an apparent need for new approaches to specifying and reporting doses for inhomogeneous dose distributions. On the one hand, there is a legitimate reservation for TCP and NTCP models. On the other hand, it is obvious that the purely dosimetric description is at best only a surrogate for biological and clinical consequences of a dose distribution.

In this article the problem of reporting and quantitatively comparing inhomogeneous dose distributions for target volumes is addressed. A new concept of Equivalent Uniform Dose (EUD) is introduced.

II. METHODS

In the following sections the development of the EUD formulas are presented in increasing order of their complexity and with an increasing inclusion of radiobiological concepts.

It is assumed that an irradiated tumor is composed of a large number of independent clonogens, and that random killing of the clonogens is well described by Poisson statistics. The binary response—control or failure—of an irradiated tumor is assumed to be determined by the expected number of surviving clonogens. Therefore, two different target dose distributions are equivalent if the corresponding expected number of surviving clonogens are equal. These assumptions lead to the idea of equivalent uniform dose:

''For any dose distribution, the corresponding Equivalent Uniform Dose (EUD) is the dose (in Gy), which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens.''

A. The simplest models

Assuming the random nature of dose deposition and independence of the cell kills, the surviving fraction (SF) of cells irradiated to a dose D is approximated by an exponential:[23]

$$\mathrm{SF}(D)=\exp\left(-\frac{D}{D_0}\right). \tag{1}$$

The dose D_0 describes radioresistance of irradiated cells and in radiobiology is called the mean lethal dose. If one prefers to describe the cell radiosensitivity using the surviving fraction at the reference dose, D_{ref} of 2 Gy (SF_2), the following obvious relationship between D_0 and SF_2:

$$\mathrm{SF}(2\ \ \mathrm{Gy})=\exp\left(-\frac{D_{\mathrm{ref}}}{D_0}\right), \tag{2}$$

gives an equivalent formula for $\mathrm{SF}(D)$:

$$\mathrm{SF}(D)=(\mathrm{SF}_2)^{D/D_{\mathrm{ref}}}. \tag{3}$$

If cells are uniformly distributed across the target volume, the overall survival fraction is the weighted average of the survival fractions taken over all (N) near-homogeneously irradiated subvolumes of the target:

$$\mathrm{SF}(\{D_i\}) = \sum_{i=1}^{N} v_i \cdot \mathrm{SF}(D_i), \tag{4}$$

where v_i is the partial volume corresponding to dose D_i. For example, a set of pairs $\{D_i, v_i\}$ defines the corresponding differential dose volume histogram. If one prefers to calculate SF ($\{D_i\}$) directly from the target dose calculation points distributed evenly within the target volume, the following formula can be used:

$$\mathrm{SF}(\{D_i\}) = \frac{1}{N} \sum_{i=1}^{N} \mathrm{SF}(D_i), \tag{5}$$

where the sum is taken over N dose calculation points.

The same fraction of cells survive if the target is irradiated uniformly to a certain unknown dose, which we propose to call the Equivalent Uniform Dose (EUD). Therefore, we postulate the following equivalency:

$$\mathrm{SF}(\mathrm{EUD}) = \mathrm{SF}(\{D_i\}). \tag{6}$$

Using formulas (3) and (4) or (5), one obtains the following formulas for EUD:

$$\mathrm{EUD}(\mathrm{Gy}) = D_{\mathrm{ref}} \cdot \frac{\ln[\Sigma_{i=1}^{N} v_i \cdot (\mathrm{SF}_2)^{D_i/D_{\mathrm{ref}}}]}{\ln(\mathrm{SF}_2)} \tag{7}$$

or

$$\mathrm{EUD}(\mathrm{Gy}) = D_{\mathrm{ref}} \cdot \ln\left[\frac{1}{N} \sum_{i=1}^{N} (\mathrm{SF}_2)^{D_i/D_{\mathrm{ref}}}\right] \Big/ \ln(\mathrm{SF}_2). \tag{8}$$

Similar simple formulas can be obtained in terms of D_0 and the corresponding equation (1).

B. Absolute volume effect

According to a simple mechanistic model of tumors (and in agreement with some clinical data), larger tumors contain more clonogens and therefore, larger doses are necessary to eradicate them.[10,11,21,25] When analyzing and comparing doses received by tumors of different sizes one may wish to relate the doses to the same reference absolute volume V_{ref}. For example, V_{ref} might be the average volume of tumors in a particular study or, any reasonable arbitrarily chosen volume. Absolute volumes can be easily incorporated into formula (4). Assuming that the number of cells is proportional to volume, the EUD can be calculated as follows:

$$\mathrm{EUD}(V_{\mathrm{ref}}) = D_{\mathrm{ref}} \cdot \ln\left[(1/V_{\mathrm{ref}}) \sum_{i=1}^{N} V_i \cdot (\mathrm{SF}_2)^{D_i/D_{\mathrm{ref}}}\right] \Big/ \ln(\mathrm{SF}_2), \tag{9}$$

where $\{V_i\}$ represents N homogeneously irradiated absolute subvolumes, each of absolute volume, V_i, receiving the corresponding doses $\{D_i\}$.

C. Nonuniform spatial distribution of clonogens

The spatial distribution of clonogens within a tumor is likely to be nonuniform. However, the distribution of clonogens is generally not known. Most often, a uniform target dose distribution is prescribed and requested. [The spatial distribution of clonogens is implicitly taken into account when the boost or the shrinking field techniques are used.] That means that clonogen nonuniformity, although known to exist, is ignored for the purpose of dose prescription. Nevertheless, if this information were available, it would be included in formula (4), and the corresponding EUD would be calculated as follows:

$$\mathrm{EUD} = D_{\mathrm{ref}} \cdot \ln\left\{\frac{[\Sigma_{i=1}^{N} V_i \cdot \rho_i \cdot (\mathrm{SF}_2)^{D_i/D_{\mathrm{ref}}}]}{\Sigma_{i=1}^{N} V_i \cdot \rho_i}\right\} \Big/ \ln(\mathrm{SF}_2), \tag{10}$$

where V_i and ρ_i are the local absolute volumes and densities of clonogens, respectively. The sum should be taken over subvolumes within which both dose and clonogen density are near-uniform.

D. Dose-per-fraction effect

Fractionation effects can be modeled using the Linear-Quadratic (LQ) model.[24] According to the LQ model, the fraction of cells surviving dose D given in N_f fractions can be calculated using SF_2 and α/β as follows:

$$\mathrm{SF}(D) = (\mathrm{SF}_2)^{\frac{D}{D_{\mathrm{ref}}} \cdot \frac{\alpha/\beta + D/N_f}{\alpha/\beta + D_{\mathrm{ref}}}}, \tag{11}$$

where D_{ref} is the reference dose per fraction of 2 Gy. It is apparent that the single hit model [formulas (1) and (3)] is a limit of the LQ model for either large α/β or, for small inhomogeneities and a dose per fraction close to the reference dose of 2 Gy.

Substituting formula (11) into the general formula (6) gives the quadratic equation for EUD:

$$(\mathrm{SF}_2)^{\frac{\mathrm{EUD}}{D_{\mathrm{ref}}} \cdot \frac{\alpha/\beta + \mathrm{EUD}/N_f}{\alpha/\beta + D_{\mathrm{ref}}}} \cdot \sum^{N} V_i \cdot \rho_i = \sum^{N} V_i \cdot \rho_i \cdot (\mathrm{SF}_2)^{\frac{D_i}{D_{\mathrm{ref}}} \cdot \frac{\alpha/\beta + D_i/N_f}{\alpha/\beta + D_{\mathrm{ref}}}}, \tag{12}$$

which can easily be solved for EUD:

$$\mathrm{EUD} = \frac{N_f}{D_{\mathrm{ref}}} \cdot \left[-\frac{\alpha}{\beta} + \sqrt{\left(\frac{\alpha}{\beta}\right)^2 + 4 \cdot \frac{D_{\mathrm{ref}}}{N_f} \cdot \left(\frac{\alpha}{\beta} + D_{\mathrm{ref}}\right) \cdot \frac{\ln A}{\ln(\mathrm{SF}_2)}}\right]. \tag{13}$$

For clarity of presentation the quantity A was defined as follows:

$$A=\sum_{i=1}^{N} V_i\cdot\rho_i\cdot(\mathrm{SF}_2)^{\frac{D_i}{D_{\mathrm{ref}}}\cdot\frac{\alpha/\beta+D_i/N_f}{\alpha/\beta+D_{\mathrm{ref}}}} \Bigg/ \sum_{i=1}^{N} V_i\cdot\rho_i. \tag{14}$$

It should be noted that both dose distributions, the original inhomogeneous dose distribution, and the equivalent uniform one, correspond to the same number of fractions, N_f. That is, the EUD in formula (13) is not expressed in terms of the reference dose per fraction. The reference dose per fraction, D_{ref}, is equal to 2 Gy and is used only in conjunction with the SF_2. That is, the cell radiosensitivity is described using the surviving fraction at that reference dose. It would be more appropriate to write it as $\mathrm{SF}_{D_{\mathrm{ref}}}$ however, we use the standard notation, SF_2, for simplicity.

E. Proliferation effect

The LQ model can be extended to include the fact that clonogens can proliferate during the course of treatment.[23,26] Assuming a constant rate of proliferation it can be shown that the overall surviving fraction for dose D given in N_f fractions over the time T is

$$\mathrm{SF}(D)=2^{[(T-T_k)/T_{\mathrm{pot}}]}\cdot(\mathrm{SF}_2)^{D/D_{\mathrm{ref}}\cdot\left(\frac{\alpha/\beta+D/N_f}{(\alpha/\beta+D_{\mathrm{ref}}}\right)}. \tag{15}$$

Here T_k is the time at which proliferation begins after the start of treatment, and T_{pot} is the potential doubling time of clonogens.

Comparing formulas (11)–(15), one can see that proliferation increases the effective number of clonogens that have to be killed to achieve local control. In this model, the effect of proliferation depends only on the overall treatment time, T, and does not depend on the other two variables of the treatment plan, that is dose, or the number of fractions. Therefore, if EUD is calculated for the same overall treatment time as the dose distribution in question, the proliferation factor cancels out, and one can use formula (11).

F. Inhomogeneity of patient population

Clonogens differ in their radiosensitivity. The apparent flattening of the dose–response curves is thought to be due to the interpatient heterogeneity.[10,11,18,23,25,27] Unless the values of the SF_2, α/β, T_k, and T_{pot} are known for the individual tumor in question, one may argue that the best guess for the EUD is the expected value of EUD taken over the patient population. For example, assuming that radiosensitivity of the population is characterized by SF_2, which is ln(−ln) normally distributed, (The Normal distribution of $\ln[-\ln(\mathrm{SF}_2)]$ is chosen because it is defined in the range $(-\infty, +\infty)$, and it is better suited for numerical integration than SF_2 itself.) the expected EUD for heterogeneous population can be calculated as follows:

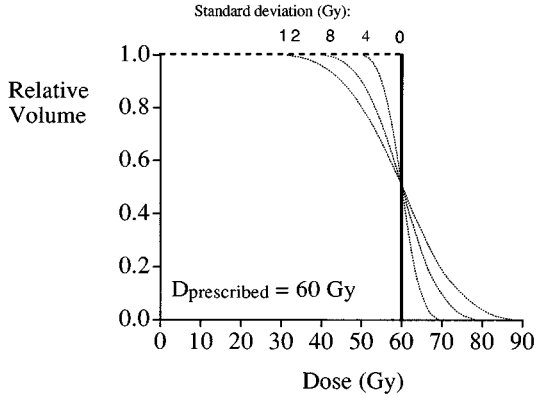

FIG. 1. A set of DVDs with various degrees of inhomogeneity of the corresponding dose distributions. The mean dose for all the dose distributions is the same and equal to the prescribed dose $D_{\mathrm{prescribed}}$.

$$\mathrm{EUD}=\frac{1}{\sqrt{2\cdot\pi}\cdot\sigma}\int_{-\infty}^{+\infty}\exp\left(-\frac{(S-\widetilde{S})^2}{2\cdot\sigma^2}\right)\cdot\mathrm{EUD}(S)\,dS, \tag{16}$$

where $S=\ln[-\ln(\mathrm{SF}_2)]$, $\widetilde{S}=\ln[-\ln(\widetilde{\mathrm{SF}}_2)]$, σ describes the width of normally distributed $\ln[-\ln(\mathrm{SF}_2)]$, $\widetilde{\mathrm{SF}}_2$ is the average SF_2 in the population in question, and EUD(S) is calculated using one of the homogeneous formulas presented earlier.

III. RESULTS

A. Test example

Figure 1 shows an example of test DVDs that were used to analyze consequences of dose heterogeneity on the EUD. The prescribed dose was 60 Gy delivered in 30 equal fractions and uniformly distributed over the target volume. The dose was calculated at 50 000 points quasirandomly covering the target volume. The dose inhomogeneity across the target volume was introduced by generating dose values according to the normal density function with the mean equal to the prescribed dose of 60 Gy and with standard deviation between 0 Gy (perfectly uniform dose distribution) up to 18 Gy (30% of the prescribed dose). The resultant DVDs have a sigmoidal shape with some cold and hot regions often present in clinical DVDs. Because the normal density function has infinite tails the lowest and the highest 1% of the generated doses were excluded from the analysis.

Figure 2 shows the EUD as a function of the standard deviation of the target dose. The EUD was calculated using three different formulas: the simplest formula (8), formula (13), which includes dose-per-fraction effects through the LQ model, and formula (16), which, in addition, includes interpatient heterogeneity. The basic formula (8) uses only one parameter—SF_2, which was arbitrarily set to 0.5. Formula (13) extends the basic formula (8) by including the dose per fraction effect and, in addition to SF_2, uses the LQ model parameter α/β, which was set to 10 Gy. For formula (16) it was assumed that $\ln[-\ln(\mathrm{SF}_2)]$ is normally distributed within a population of tumors with the mean SF_2 of 0.5 and

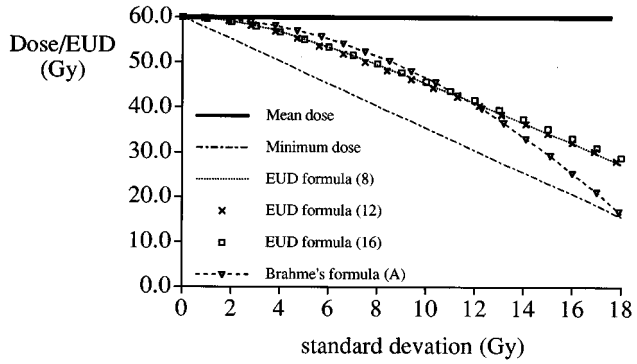

FIG. 2. EUD as a function of the standard deviation of the mean target dose, calculated using three different formulas for EUD and the Brahme's formula. The minimum and the mean doses are shown for comparison.

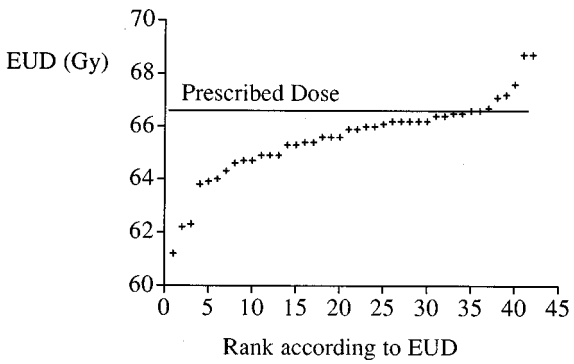

FIG. 3. The EUDs for 42 patients with a prescribed dose of 66.6 Gy, ranked according to their EUD.

the σ of 0.1. The formulas (8), (13), and (16) contain, respectively, one, two, and three free parameters. The dashed line with triangles represents the calculation of EUD according to the new Brahme's formula with D equal to 60 Gy, and P (60 Gy) set to 0.5. To make the two approaches to EUD comparable, the third parameter of Brahme's formula, γ_{50}, was estimated from the formula $\gamma_{50}=-0.25\cdot\ln(2)\cdot\mathrm{TCD}_{50}\cdot\ln(\mathrm{SF}_2)$.[10] Assuming SF_2 of 0.5 and TCD_{50} of 60 Gy the corresponding γ_{50} is 7.2. The average and the minimum doses are also shown to illustrate their relation to the EUD.

B. Clinical example

The concept of EUD has been applied to a group of 42 patients with chordomas of the base of the skull. The prescribed dose for all patients was 66.6 Gy delivered in 37 fractions of 1.8 Gy per fraction. Due to the constraints on the maximum allowed doses to the spinal cord, the brainstem, the optic nerve, and chiasm, it was not always possible to deliver the prescribed dose uniformly. (The mean delivered dose was in the range ⟨65 Gy, 68 Gy⟩ and the standard deviation was in the range ⟨0.3 Gy, 6.1 Gy⟩.) The planner, using a modern CT-based three-dimensional treatment planning system and the conventional trial-and-error planning technique has developed the best plans under the given circumstances.

Figure 3 shows the calculated EUDs for all the patients ranked according to the corresponding EUD. The EUDs have been calculated using formula (13) with SF_2 arbitrary chosen to be equal to 0.5 and α/β of 10 Gy. For comparison, the EUDs were also calculated using the simplest one-parameter formula (7). The maximum difference between the corresponding EUDs calculated with formula (13) (which takes into account the dose per fraction effect) and formula (7) was less than 0.7 Gy. The range of EUDs for this group of patients is 61.2–68.7 Gy (which corresponds to dose per fraction of 1.65–1.86 Gy), with a majority of the EUDs being below the prescribed dose of 66.6 Gy.

Figure 4 shows two examples of DVDs that were ranked 4th and 39th in Fig. 3 with the corresponding EUDs of 63.8 and 67.3 Gy. The difference between the two EUDs is larger than the difference between the corresponding mean doses (65.4 and 67.6 Gy, respectively). The difference between the minimum doses is even larger (56.2 vs 61.8 Gy).

IV. DISCUSSION

Figure 2 shows that the predictions of the simplest one-parameter model of EUD [formula (8)] are very similar to the predictions of the more complex models, which include the dose per fraction effect [formula (13)] and interpatient heterogeneity [formula (16)]. The correction for the dose per fraction is very small (less than 1%) because the EUD is defined as the total dose given in the same number of fractions as the original dose. That is, the EUD is normalized to the fixed number of fractions, not to the fixed dose per fraction. Therefore, the corrections for the dose per fraction effect due to dose inhomogeneity tend to cancel out. In order to compare two or more studies where different fractionation regimes were used, one needs to normalize all the analyzed EUDs to the same number of fractions or to the same dose per fraction. If one wants to normalize the EUD to the reference dose per fraction, d_{ref}, the following LQ-based translation formula can be used:

$$\mathrm{EUD}_{d_{\mathrm{ref}}}=\mathrm{EUD}_{N_f}\cdot\frac{\alpha/\beta+\mathrm{EUD}_{N_f}/N_f}{\alpha/\beta+d_{\mathrm{ref}}},\tag{17}$$

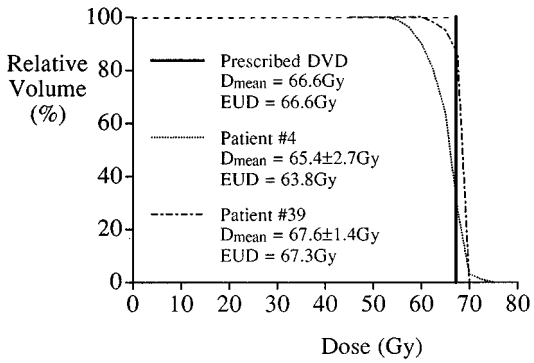

FIG. 4. The DVDs ranked 4th and 39th of the 42 DVDs evaluated in Fig. 3. The prescribed DVD is shown for comparison.

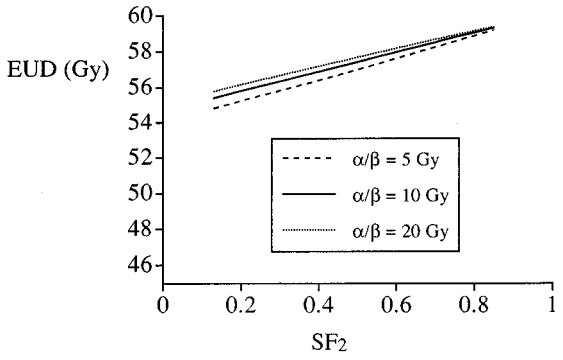

FIG. 5. The EUD as a function of the SF_2 for three levels of α/β.

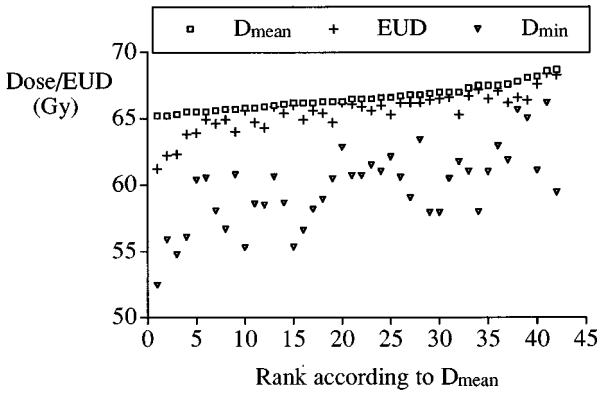

FIG. 7. The comparison of the EUDs, mean doses, and minimum dose for 42 patients. The patients were ranked according to their mean target dose.

where EUD_{N_f} denotes the EUD normalized to a fixed number of fractions and $EUD_{d_{ref}}$ denotes the EUD normalized to a fixed dose per fraction. When two studies have different overall treatment times the clonogen proliferation effect [formula (15)] ought to be considered. It is important to recognize the difference between the two types of normalization, since the calculated EUDs may differ substantially if the dose per fraction actually delivered (that is, EUD_{N_f}/N_f) is different from the reference dose per fraction, d_{ref}. Note, that d_{ref} is not related to D_{ref} used in conjunction with the SF_2, although both doses can be equal.

The correction for interpatient variation is also very small—less than 1%, and is fairly insensitive to the level of interpatient heterogeneity. That is, the population-average EUD is very well approximated by the EUD calculated for the average SF_2. This is due to the fact that the distribution of EUDs is unimodal and fairly symmetrical. Note that the distribution of the corresponding TCP's is typically bimodal (with a majority of the TCPs either close to 0 or 1) and asymmetrical.

The robustness of the EUD concept is further illustrated in Figs. 5 and 6. The EUD was calculated for a target inhomogeneously irradiated to a mean dose of 60 Gy in 30 equal fractions. The shape of the corresponding DVD was similar to that in Fig. 1, with the standard deviation equal to 5 Gy. Figure 5 shows the EUD calculated using formula (13) as a function of SF_2 for three values of α/β. Figure 4 shows the EUD as a function of α/β for three levels of SF_2 for the same conditions.

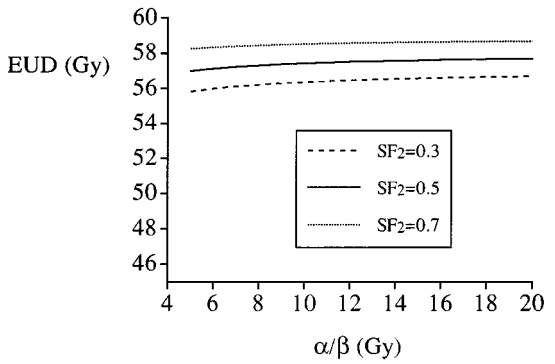

FIG. 6. The EUD as a function of the α/β for three levels of SF_2.

Figure 2 suggests that for relatively small dose inhomogeneity (say, less than 2 Gy or 3% of the typical mean target dose) the mean target dose might be a good approximation to EUD—as Brahme suggested using similar arguments.[6,8] Figure 7 shows again the clinical dataset shown in Fig. 3 with the corresponding mean and minimum doses. It is apparent that EUD is always larger than the minimum dose, and is always less than the corresponding mean dose. The three doses are equal only in the case of a perfectly homogeneous dose distribution. Figure 7 also suggests that the minimum target dose can significantly underestimate the dose actually delivered, if the cold spot is very small. For example, in the case ranked first in Fig. 7, the minimum target dose is ~15% less than the EUD, and ~20% less than the mean target dose. The range of minimum doses in Fig. 7 is much larger than the range of mean doses or EUDs. This is due to the fact that, in many cases, there is a gradient of dose at the periphery of the target volume, and the corresponding DVDs approach the 100% volume level almost tangentially. In such cases, the minimum target dose may correspond to just one or two voxels of the target volume. It should be emphasized that the effect of a cold spot depends not only on the amount of underdosing but also on the size of the cold spot. Surely, it also depends on the model parameters.

Clinically observed dose–response curves are less steep than might be deduced from Poisson statistics.[23] Most often it is attributed to inhomogeneity of the patient population in their response to radiation treatment. Bentzen reported that better stratification of patients results in steeper observed dose–response curves.[25,26] Figure 7 shows yet another cause for flattening dose–response curves. The prescribed dose for all 42 patients was 66.6 Gy, and the same dose was also recorded as the dose actually delivered. Therefore, for retrospective statistical analysis, it was assumed that the whole group received the same dose. Figures 3 and 7 show that, according to the EUD concept, there is a real spread of doses actually delivered (~10% of the prescribed dose). Therefore, the dose response of the whole group is flattened. Applying

the EUD concept reveals the finer structure of the analyzed group of patients with respect to the received dose. Because the EUD is calculated for each individual dose distribution, it is well suited for model fitting using the powerful maximum-likelihood method.[13,22]

Flattening of the dose–response curves is also due to variations in the irradiated volume. Assuming that larger tumors contain more clonogens, the same dose is less effective for the larger tumors than it is for the smaller ones. When tumors of different sizes are grouped together, the observed dose–response relationship is shallower than it would have been, had the tumors been stratified according to their size.[26] In the EUD approach each tumor is analyzed individually, and the absolute volume effect is modeled by assuming that the number of clonogens is proportional to the absolute volume [formula (9)].

Figures 5 and 6 demonstrate that for an inhomogeneous dose distribution the corresponding EUD is a slowly and almost linearly increasing function of SF_2, and that the EUD is a very slowly increasing function of α/β (in the range typical for tumors). That is, the knowledge of the exact value of α/β or SF_2 for an individual is not crucial for estimating the EUD. The attraction of the EUD concept is also demonstrated in Fig. 2. The EUD is quite robust as a function of the underlying biological models and parameters (which are known to a lesser degree), but is a sensitive function of dose and volume variables (which can be measured quite accurately). Figure 2 also suggests that, in most situations, one can use the simplest models of EUD [formulas (7)–(9)] without sacrificing much of the accuracy. The simplest model uses only one parameter, that is the SF_2 (or D_0).

The concept of EUD and the concept of D_{eff} developed by Brahme are based on similar assumptions, but the EUD differs from the D_{eff} in one important aspect. The EUD describes the potential of a dose distribution to kill cells in a stochastic multifraction manner, but alone does not determine the probability of local control. For the same reason that a given physical dose do not correspond to any particular value of TCP. The TCP can be estimated from a EUD (or a dose) if more information is available—the most important one being the size, or the number of clonogens, of the target in question. By retrospective analysis of EUDs and the corresponding outcomes of treatment, one can estimate the corresponding dose–response curve. That is, the probability of tumor control as a function of EUD. On the other hand, in order to calculate the Brahme's D_{eff}, one needs to know heretofore the TCP as a function of dose. One may argue that if we were able to calculate the TCP for any dose distribution, we would not need to know the corresponding uniform dose D_{eff} (or EUD).

The concept of EUD may be also applicable to brachytherapy dose distributions, although one would need to take into account the dose-rate effect. The brachytherapy dose distributions can be extremely nonuniform. It is easy to see that small and very hot spots around the sources of radiation will not contribute much to the overall EUD because of the saturation effect for a single subvolume, and because of the averaging of the effect over the entire target volume.

The EUD can be also used as an objective (score) function in computer optimization of treatment planning. The EUD should be maximized subject to dose and dose-volume constraints on normal tissues. Of the two plans both satisfying the normal tissue constraints, the one with higher EUD represents higher probability of local control. However, it is important to remember that the clinical importance of a difference in EUD cannot be determined without additional knowledge relating the EUD to the probability of local control. That is, without knowing the position and the slope of the dose–response function. Hopefully, the application of the EUD concept will help in determining dose–response relationships. Although not intended for that purpose, the EUD can also be used to compare the effectiveness of different fractionation schemes. A fractionation regime that corresponds to higher EUD is judged to be more effective in terms of the probability of local control.

V. CONCLUSIONS

The concept of EUD was developed to take into account the unavoidable inhomogeneity of clinical dose distributions. The concept stems from the basic radiobiological principles, yet is very simple and easy to use for reporting doses actually delivered to the patients under actual treatment conditions. The application of the EUD formalism to a clinical dataset of 42 cases revealed a significant variation in the doses actually delivered as compared to the prescribed doses. It is apparent that one of the causes for flattening dose–response curves is inadequate reporting of doses actually delivered. The EUD should be a better single predictor of outcome of radiotherapy than several other strictly dosimetric measures commonly used.

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