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Characterization of Dose Distributions Through the Max and Mean Dose Concept

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A new approach for the determination of the equivalent uniform dose (EUD) for inhomogeneously irradiated normal organs is developed and tested. The EUD is calculated as a linear combination of the maximum and the mean dose: $EUD = \alpha D_{\max} + (1-\alpha)\bar{D}$. We call this the max & mean model. The values of α are determined by a fit to the Emami tables for complication levels of 5% and 50%. The predictions of the max & mean model are compared with the Emami tables for different treatment volume fractions. The quality of the fit is also compared with the well-known power-law EUD model. The max & mean model makes it possible to make useful predictions of the EUD for organs having an organization anywhere between serial and parallel. The model can be fitted to the Emami tables within the same error range as the widely used power-law model (about 10%) and can be integrated into linear multicriteria optimization algorithms for planning of intensity-modulated radiotherapy.

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Even with the most sophisticated radiotherapy techniques, delivery of some of the dose to healthy normal structures surrounding the tumor target volume is unavoidable. The goal is to keep this undesired dose within tolerance. The effect of the dose delivered to normal organs depends not only on the dose level but also on the spatial dose distribution, which is generally non-uniform. Some organs tolerate high dose values in small subvolumes, if the rest of the organ is spared. These organs have a *parallel* structure: the function is preserved even if a certain fraction of the organ is destroyed. A typical example is the lung. In the other category of organs, high doses are harmful even if they are limited to small volumes—the organ structure is *serial*. A typical example of this is the spinal cord.

In treatment planning, and particularly in computer-aided plan optimisation, it is desirable to characterize the dose effect in the relevant organs by a single number rather than the complex spatial dose distribution. One attempt to accomplish this is based on the 'effective dose' (1) or 'equivalent uniform dose' (EUD) (2, 3), which is defined as the uniform dose that would lead to the same effect as the given non-uniform dose. A known derivation of the EUD for arbitrary organs is based on the so-called 'volume effect', which is the dependence of the tolerance dose on the treated volume. A widely used formula to describe the volume effect is the power-law relationship $TD(v) = TD(1)/v^n$ (4). Here, $TD(1)$ is the tolerance dose if the whole organ is treated uniformly, and $TD(v)$ is the tolerance dose if the fraction v is treated and $1-v$ gets no dose. This is clearly an idealization because such binary distributions never occur in reality. In any case, from this power-law relationship it follows that the EUD can also be written as a power-law: $EUD = (\Sigma_i v_i D_i^{1/n})^n$ (cf. (3, 5, 6)). For many organs, the value of n has been fitted to the Emami tables (7, 8). For parallel organs such as the lung, the exponent n is close to 1 (i.e. the EUD equals the mean dose) and for serial organs n is close to 0 (i.e. the EUD equals the maximum dose). The spectrum of n-values ranges from 0.01 (serous otitis) to 0.85 (lung pneumonitis). Obviously, the values can be different for different clinical endpoints.

In this study we sought to establish an even simpler approach to describe the EUD, based on the work by Dale & Olsen (9), who reported that the normal tissue complication probabilities of purely serial and purely parallel organs at risk correspond to the maximum dose and the mean dose in the organ, respectively. For organs with a mixed serial and parallel structure, Dale & Olsen suggested using a linear combination of the maximum and the mean

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dose. We call this the max & mean dose approach. The goal of this work is to determine the organ-specific parameters for this approach, and to investigate and test the hypothesis.

MATERIAL AND METHODS

The following linear max & mean model is used to represent the EUD:

$$EUD = \alpha D_{\max} + (1-\alpha)\bar{D}. \quad [1]$$

$D_{\max}$ is the maximum and $\bar{D}$ the mean dose of the radiation delivered to the organ. α is an organ-specific parameter ranging from 0 to 1.

We calculated values of α and EUD by a fit to the Emami tables (7). In Emami et al's paper, tolerance doses (TD) for various organs were presented depending on the irradiated relative volume v (whereby v takes values of $v_1 = 1/3$, $v_2 = 2/3$ and $v_3 = 1$) and on two levels of complication rate (5% and 50%, in the following specified as $TD\,5$ and $TD\,50$) 5 years after treatment. For each complication rate, the associated maximum and mean dose can be determined straightforwardly: because the fraction v gets the dose TD and the fraction $(1-v)$ gets no dose, the maximum dose is given as $D_{\max} = TD$ and the mean dose is given as $\bar{D} = v \cdot TD$.

From these data we can deduce the organ-specific parameter α, which should be independent of the complication rate, and two EUD-values ($EUD\,5$ and $EUD\,50$), applying to a complication rate of 5% and 50%, respectively. To perform the fit, we rewrite the max & mean model as $\alpha(\bar{D} - D_{\max}) + EUD = \bar{D}$ and build an overdetermined equation system for each individual organ:

$$\begin{pmatrix} (1-v_1)\cdot TD\,5(v_1) & 1 & 0 \\ (1-v_2)\cdot TD\,5(v_2) & 1 & 0 \\ (1-v_3)\cdot TD\,5(v_3) & 1 & 0 \\ (1-v_1)\cdot TD\,50(v_1) & 0 & 1 \\ (1-v_2)\cdot TD\,50(v_2) & 0 & 1 \\ (1-v_3)\cdot TD\,50(v_3) & 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} \alpha \\ EUD\,5 \\ EUD\,50 \end{pmatrix}$$

$$= \begin{pmatrix} v_1 \cdot TD\,5(v_1) \\ v_2 \cdot TD\,5(v_2) \\ v_3 \cdot TD\,5(v_3) \\ v_1 \cdot TD\,50(v_1) \\ v_2 \cdot TD\,50(v_2) \\ v_3 \cdot TD\,50(v_3) \end{pmatrix}. \quad [2]$$

This can be abbreviated as $A \cdot x = c$, and a least-square fit of the three parameters α, $EUD\,5$ and $EUD\,50$ can be performed by calculating $x = (A^T A)^{-1} A^T c$. The rows of the transposed matrix A^T consist of the columns of the matrix A. In textbooks on linear algebra, more details and proof of this technique can be found. As errors, we used the mean quadratic deviation of all meaningful quadratic subsystems (i.e., subsystems with 3 equations) from the least-square fit. 'Meaningful' is defined as those subsystems that lead to an exact solution for α, $EUD\,5$ and $EUD\,50$ (e.g. it is not meaningful to select the first three lines of the above equation system, because there would be no solution for $EUD\,50$).

With regard to the simple data structure provided by (7), the universal formulation of the power-law model,

$$EUD = \left(\sum_i v_i D_i^{1/n} \right)^n, \quad [3]$$

can be simplified to $EUD = v^n \cdot TD$, which leads to values for n and EUD in a very similar way as for the max & mean model.

RESULTS

The results of the fits (the particular clinical endpoints are only noted for organs with more than one endpoint, the others can be found in (7)) are presented in the Table 1. For the larynx (endpoint edema) and the brain stem, only data for a complication rate of 5% are provided. Wherever no error is listed in the Table, only two TD-values are given in (7), making the fit mathematically exact.

Once the values of α and EUD respectively n and EUD have been fitted, the tolerance dose $TD(v)$ of an arbitrary irradiated fraction v can be calculated. To compare the power-law model with the max & mean model, we plotted the tolerance dose $TD(v)$ as a function of the irradiated fraction v. These plots for the lung ($\alpha = 0.09$, $n = 0.85$), the

Table 1

Fitting the max & mean model to the data by Emami et al. (7)

Organ	α	EUD5 [Gy]	EUD50 [Gy]
Larynx (necrosis)	0.83 ± 0.13	68.6 ± 4.1	78.3 ± 4.1
Larynx (edema)	1.00	45.0	
Lung I	0.09 ± 0.09	18.7 ± 2.4	26.0 ± 2.9
Heart	0.53 ± 0.12	39.7 ± 2.9	48.2 ± 3.0
Esophagus	0.90 ± 0.03	55.7 ± 0.7	67.6 ± 0.9
Stomach	0.83 ± 0.07	51.7 ± 2.2	63.5 ± 2.6
Small intestine	0.80 ± 0.09	41.7 ± 2.5	53.6 ± 4.3
Colon	0.75 ± 0.02	45.4 ± 0.7	54.6 ± 0.8
Liver	0.50 ± 0.12	30.8 ± 3.0	38.0 ± 2.9
Kidney I	0.17 ± 0.08	22.4 ± 0.8	28.5 ± 1.0
Bladder	0.64 ± 0.19	67.7 ± 4.5	77.4 ± 4.7
T-M joint mandible	0.89 ± 0.08	59.4 ± 2.3	71.0 ± 2.6
Brain	0.67 ± 0.06	45.4 ± 1.8	58.7 ± 1.9
Brain stem	0.75 ± 0.04	49.5 ± 1.0	
Brachial plexus	0.96	60.1 ± 0.2	74.9 ± 0.2
Ear mid/ext (acute)	1.00 ± 0.0	30.0	40.0
Ear mid/ext (chronic)	1.00	55.0	65.0
Parotid I and II	1.00	32.0	46.0

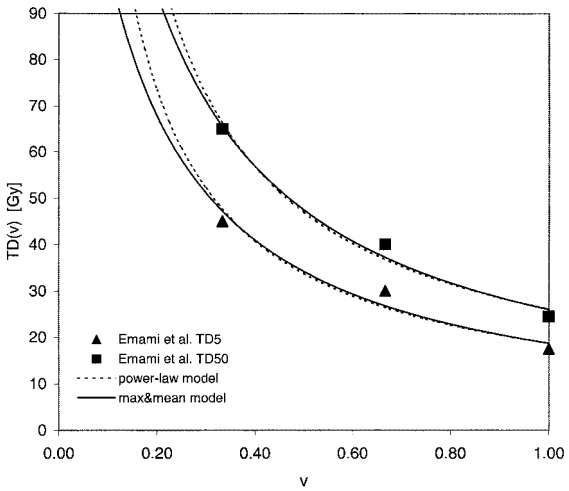

Fig. 1. Tolerance doses of the lung in dependency on the irradiated volume fraction v. Shown are the discrete values give by Emami et al. (7) and the comparison of the two EUD models described in this paper.

heart ($\alpha = 0.53$, $n = 0.34$) and the esophagus ($\alpha = 0.90$, $n = 0.06$) are shown in Figs. 1 to 3, representing different organ structures from 'mostly parallel' to 'mostly serial'. Both models fit the data within a tolerance level of about 10%.

DISCUSSION

The results show that the max & mean model can be fitted to the Emami tables with the same accuracy as the standard power-law relationship. A single value of α suffices to characterize most organs at different tolerance dose levels. Whether the model can also be fitted to real clinical data remains to be seen, when more data become available. It should be noted that all error ranges shown in this paper are the fit errors with respect to the Emami tables (7). The errors of the Emami data themselves, which for some organs are highly speculative, are not considered.

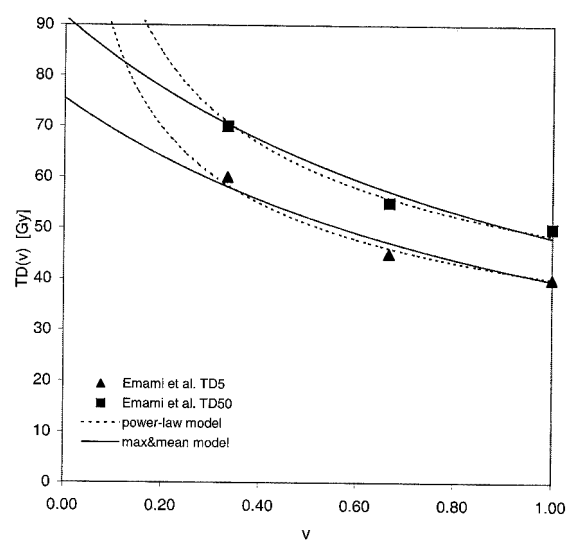

Fig. 2. Same as Fig. 1, for the case of the heart.

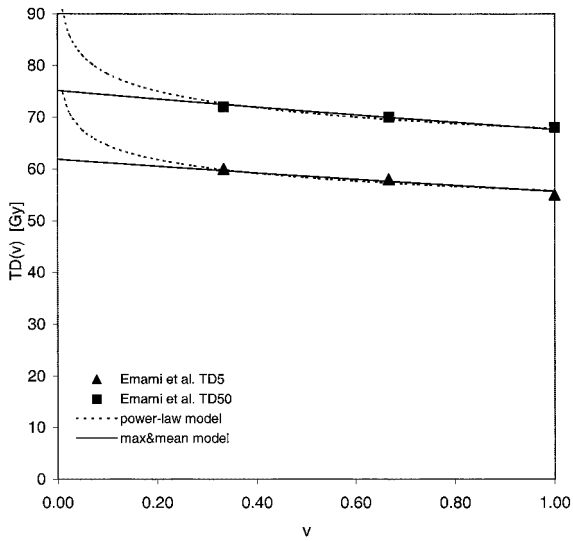

Fig. 3. Same as Fig. 1, for the case of the esophagus.

From Fig. 3 in particular, it is obvious that the max & mean model differs from the power-law model in the case of small, treated subvolumes. Mathematically, this is clear because the power-law expression for the tolerance dose has a pole at $v = 0$, i.e. according to this model, small subvolumes can be treated with extremely high doses. This is not the case for the max & mean model, which is sensitive to small hot spots. On the one hand, this can be advantageous: if the model is used for plan evaluation in inverse treatment planning, overdosages in small sub-volumes of a serial organ can be effectively reduced; in some cases the use of the power-law model or quadratic deviations from a subscribed physical dose do not penalize such overdosages strongly enough. On the other hand, an organ at risk lying directly next to the tumor target volume has to get a high dose at the border in order to achieve the curative dose in the tumor volume. High doses in very few organ voxels should therefore be made possible.

So a reasonable way to deal with the characteristics of the max & mean model is through the appropriate determination of D_{max}: this should be identified with the highest mean dose over a certain sample volume, e.g. about 1.5 cm^3, rather than the highest dose value of one single point. This definition follows ICRU 50 (10) and ensures that the dose values in areas with a steep dose gradient (i.e. at the border of organs at risk lying directly next to the target volume) are not overestimated.

Again, also for small, treated subvolumes, more clinical data are desirable for a better evaluation of the different models.

One main advantage of the max & mean EUD concept is its linearity. It allows a linear multicriteria model for the optimization of fluence profiles, especially for the inverse planning of intensity-modulated radiotherapy, in the following setting: subject to the constraints

$$EUD\,(D_k) \le U_k(1+t_k),\ k=1,\ldots,K \quad \text{'risk constraints'} \quad [4]$$

and

$$Min(D_T) \ge L(1-t) \quad \text{'target constraints'}, \quad [5]$$

independently minimize the objectives

$$t_k \to \min,\ k=1,\ldots,K; \quad t \to \min. \quad [6]$$

Here, the numbers U_k are ideal tolerance doses for organs at risk while L is an ideal curative dose for the target volume.

This linear model has good numerical properties and can readily and quickly be solved with standard linear programming tools for various solution concepts of multicriteria optimization. In (11), a Pareto solution setting of the model given above is described and discussed in more detail.

Another benefit of the max & mean approach is that it can be applied to retrospective data even if the maximum and the mean doses only are known. However, for organs with a steep dose gradient, it is important to know the exact definition of the maximum dose.

It remains to be investigated whether a similar approach can also be used to characterize the dose distribution in the tumor target volume. Obviously, since here the minimum dose is more relevant than the maximum dose, one should rather use a 'min & mean' approach.

CONCLUSION

According to the presently available (Emami) data, the equivalent uniform dose in normal structures can be expressed with a simple model using a linear combination of the maximum and the mean dose. It is as good as the existing models and it allows the application of efficient linear multicriteria optimization algorithms in inverse planning for intensity-modulated radiotherapy.

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