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Ranking radiotherapy treatment plans: physical or biological objectives?

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Background. *The ranking of treatment plans in radiotherapy is of importance when there are alternative approaches to treating an individual patient, in assessment of dose information collected during clinical trials and in formulation of objectives for optimization routines.*
Methods. *Several physically and radiobiologically-based dose indices were calculated for a series of model dose-volume histograms (DVHs). The ranking of these DVHs according to each dose index was examined. Variation in the ranking of the radiobiological indices with parameters used in the models was also examined. Ranking according to the indices was also examined for DVHs of planning target volumes (PTVs) for a series of 18 patients treated with external beam radiotherapy for prostate carcinoma.*
Results. *It was found for both the model and real DVHs that treatment plan ranking depends explicitly on the model used for ranking target-volume doses (i.e., the dose index used). For the radiobiological models, there is a strong dependence of DVH ranking on the radiobiological parameters used in the models (specifically, the 'alpha' value from the linear-quadratic model).*
Conclusion. *When ranking radiotherapy treatment plans during planning or in evaluation of clinical trials, attention should be paid to the models used in dose evaluation.*

Key words: radiotherapy planning, computer assisted; radiobiology

Introduction

Many situations arise in radiotherapy treatment planning where multiple treatment plans need to be compared in order to evaluate the optimal plan, or in order to provide a direct comparison of the relative merits of each of the plans. Such situations arise during:

- The treatment planning process for an individual patient. If two or more irradiation strategies are available, it will be necessary to decide which is the best strategy.
- During evaluation of dosimetric data collected during clinical trials. In order to correlate treatment outcome with delivered dose, a method of describing dose distributions to target volumes must be used.

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- During inverse planning optimization procedures. Inverse planning requires specification of an objective function which describes the optimality of a given dose distribution. Successive optimization iterations require a comparison of treatment plans on the basis of that objective function.[1-3]

In order to perform the plan comparison in terms of the dose distribution delivered to the target volume (the PTV encompassing the tumor volume), indices need to be stated which reduce the complex distribution of dose/volume throughout the PTV to a single scalar value. The dose distribution is frequently presented in the form of a dose-volume histogram (DVH), which can be easily reduced to a single index (a 'dose index') by computational methods.

Several alternatives exist for dose indices. In purely physical terms, the delivered radiation doses can be treated as quantities, which directly relate to treatment outcome. In this case, 'physical objectives' are used to describe the optimality of a treatment plan. An alternative is to attempt to relate the physical dose distribution more directly to some actual indication of probable response. In this case, we are using a 'radiobiological objective', which will be based upon some hypothesized (possibly validated) model for cellular response.

The usefulness of either physical or radiobiological dose indices depends very much on the correlation of those indices with treatment outcome. Such validation requires evaluation of data from large-scale clinical trials. In relating dose indices to each other, it is important to consider whether individual dose indices will rank alternative treatment plans differently, and whether that ranking will depend on the specifics of the models themselves. This study aimed at examining those differences and dependencies.

Methods

Dose indices considered

A series of physical dose indices were used. These were:

- mean dose;
- minimum dose;
- maximum dose;
- dose standard deviation; and
- least-squares deviation from prescription dose.

The radiobiolgically-based indices (DVH reduction values) considered were:

- tumour control probability (TCP); [4,5] and
- equivalent uniform dose (EUD). [6-8]

Both of these models were based on the linear-quadratic approach to describing cell kill, ignoring time and fractionation effects and assuming independence of all tumor cells. Thus, for a DVH described by a distribution of N doses, d_i, at discrete volumes, v_i, for a tumor with uniform cell density ρ, the equations used for TCP are:

$$TCP = \frac{1}{K}\sum_{m=1}^{K}\exp\left[-N_s\right], \qquad (1)$$

with

$$N_s = \prod_{i=1}^{N}\rho v_i \exp\left[-\alpha_i d_i\right]. \qquad (2)$$

Equation (1) provides population averaging by sampling TCP over a large range (K - typically 10^4) described by a normal distribution of alpha-values defined by a mean alpha value, α_m, and a standard deviation, α_σ. For EUD, population sampling is not necessary (Ebert, 2000) and the equation for EUD is:

$$EUD = \frac{-1}{\alpha}\sum_{i=1}^{N}\exp\left[v_i \exp\left(-\alpha_m d_i\right)\right], \qquad (3)$$

where N is the number of bins in the DVH. In all calculations, parameter values of α_σ = 0.1 Gy^{-1} and $\rho = 10^8$ cells/cm^3 were used. Values of α_m in the range 0.05 Gy^{-1} to 0.8 Gy^{-1} were considered.

The physical and radiobiological indices listed above were calculated for a series of model and real DVHs in order to examine how those DVHs were ranked according to each index.

Model DVHs

A series of artificial DVHs were considered (Figure 1) which represented a large range of possible dose-volume conditions in a PTV. These distributions are:

1. A normal (Gaussian) distribution with a standard deviation of 5% of the prescription dose.
2. A normal distribution with a standard deviation of 10% of the prescription dose.
3. A single-sided normal distribution with a standard deviation of 10% of the prescription dose.
4. Uniform dose delivery except for a hot spot of 150% over a volume of 5%.
5. Uniform dose delivery except for a cold spot of 50% over a volume of 5%.

For all model DVHs a tumor volume of 100 cm^3 and a mean dose of 60 Gy was used.

DVHs for prostate treatments

Figure 2 shows DVHs for PTV for 18 patients treated with external beam radiotherapy for prostate carcinoma (follow-up information pending).

Results

Model DVHs

For the model DVHs, data has been summarised in Figure 3. For each dose-index, the value has been shown for each DVH. The ranking of the DVHs according to each index is also shown. Figure 4 shows the variation in TCP and EUD for each of the model DVHs with variation in the value of α_m.

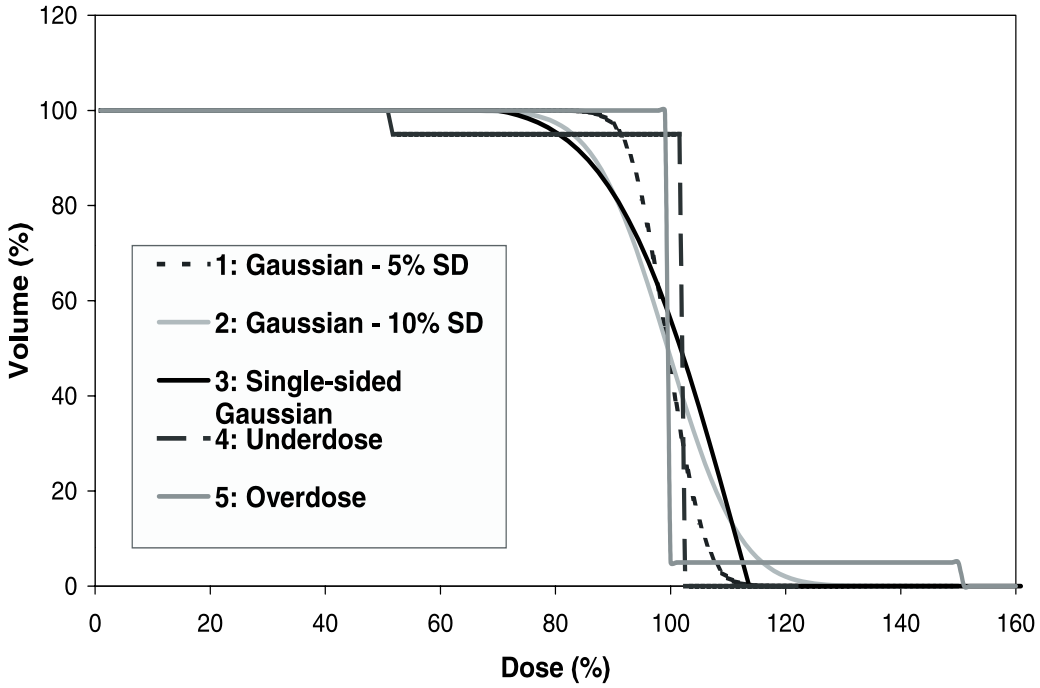

Figure 1. Model DVHs used to represent a broad range of feasible dose distributions.

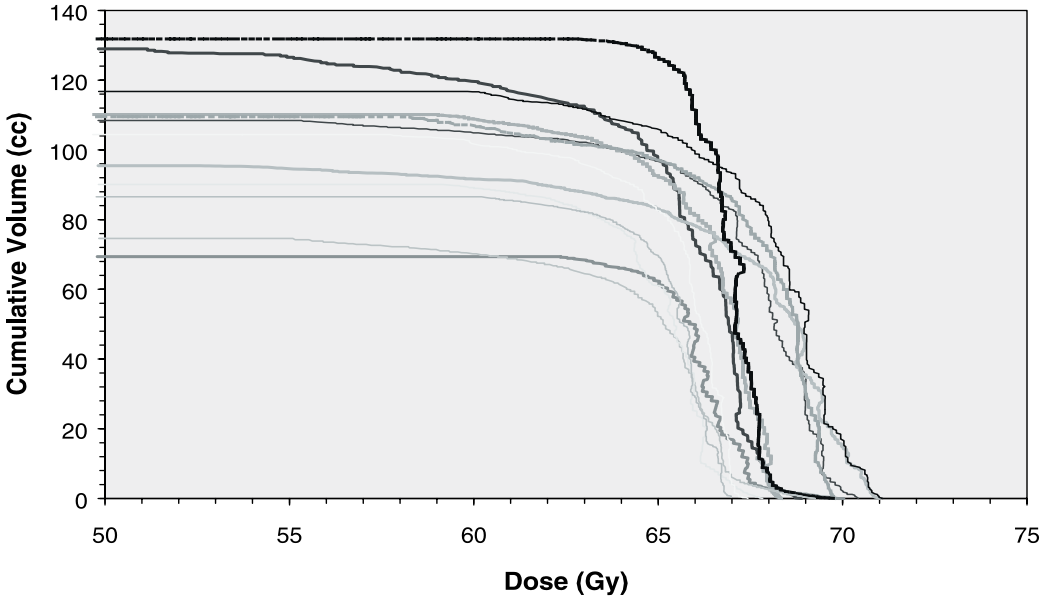

Figure 2. DVHs for PTV for 18 patients treated with external beam radiotherapy for prostate carcinoma. Prescription dose was 66 Gy (100 % level) for all cases.

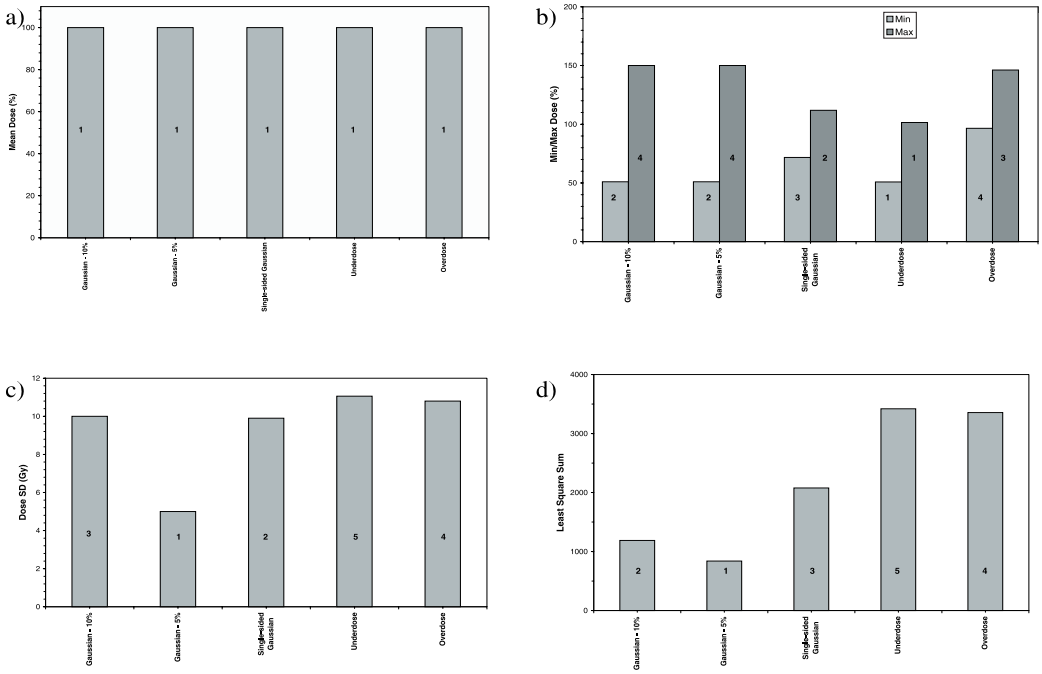

Figure 3. Summarized results for physical dose-indices for the five model DVHs. a) Mean dose, b) Maximum/Minimum dose, c) Dose standard deviation, d) Sum of least-squares. The numerals show the order of DVH ranking according to each dose-index.

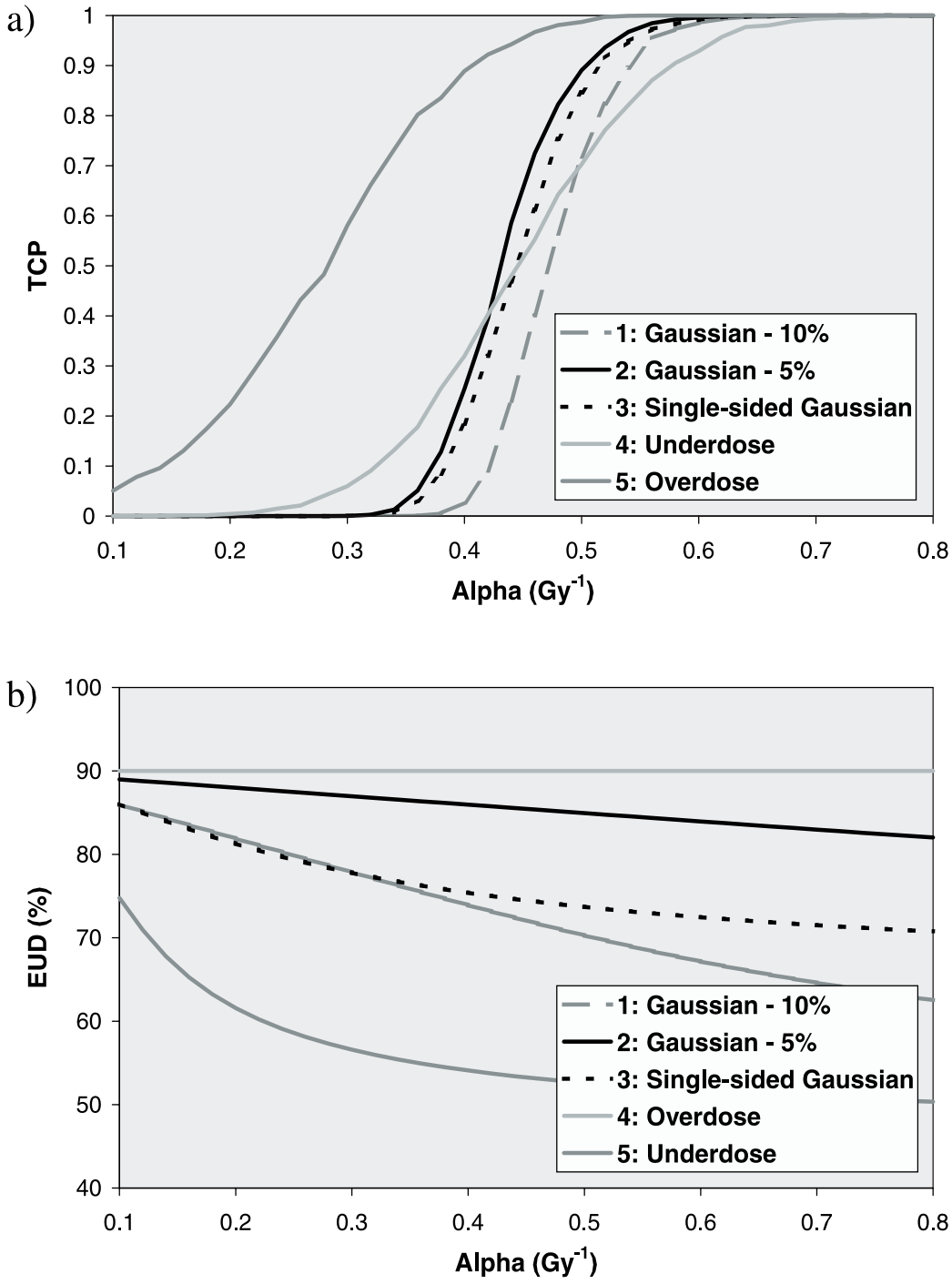

Figure 4. Variation in values of a) TCP and b) EUD with alpha (Gy^{-1}) value, showing some overlap in the order of DVH ranking.

DVHs for prostate treatments

In order to visualize the ranking of the 18 prostate-patient DVHs according to the physical dose-indices, the DVHs were ordered according to one of the indices, and all indices plotted together. Thus in Figure 5a, the DVHs have been ordered according to their mean dose. The figure then shows how the DVHs

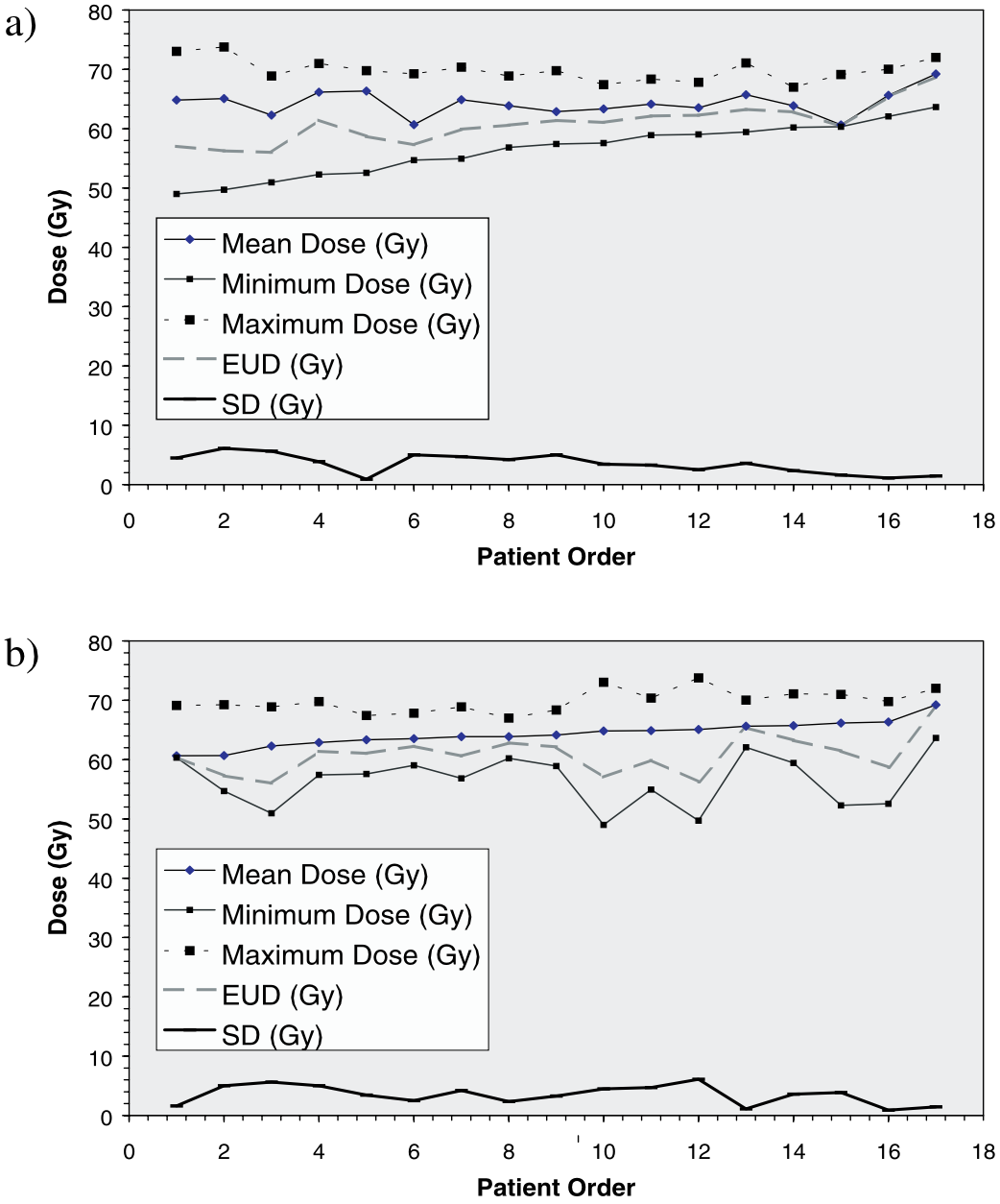

Figure 5. Variation in physical dose-indices across all 18 patients DVHs. a) Data sorted by increasing mean dose, b) data sorted by increasing minimum dose. EUD values calculated using α_m = 0.35 Gy^{-1}.

compared according to the other dose-indices. Figure 5 b shows the same information with DVHs ranked according to minimum dose.

Figure 6 shows variation TCP and EUD values for all 18 DVHs as they vary with mean alpha value in the respective radiobiological models.

In Figure 7, the ranking of the 18 DVHs according to TCP or EUD has been shown using an intensity scale at each value of α_m.

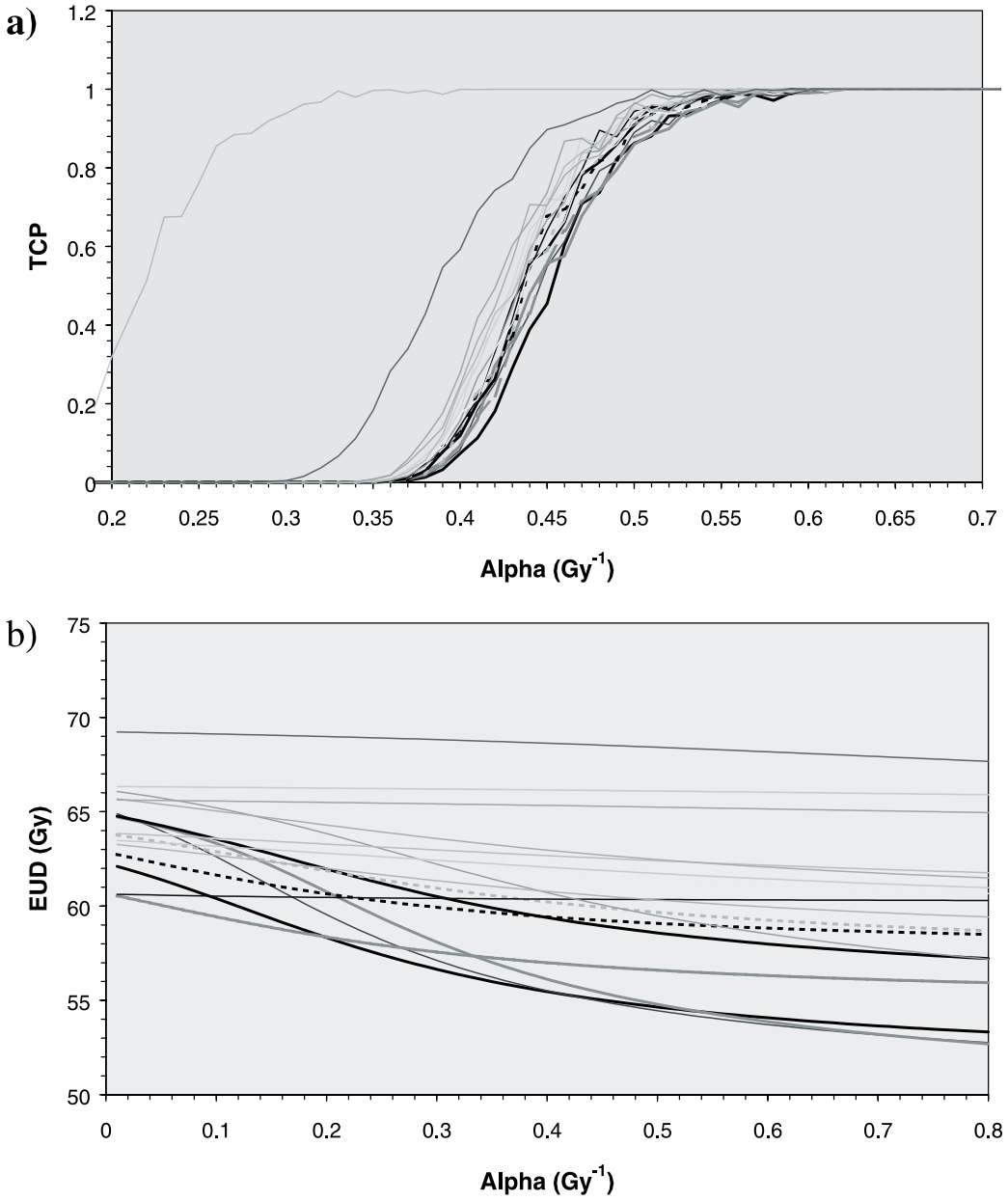

Figure 6. Variation in values of a) TCP and b) EUD with alpha (Gy-1) value.

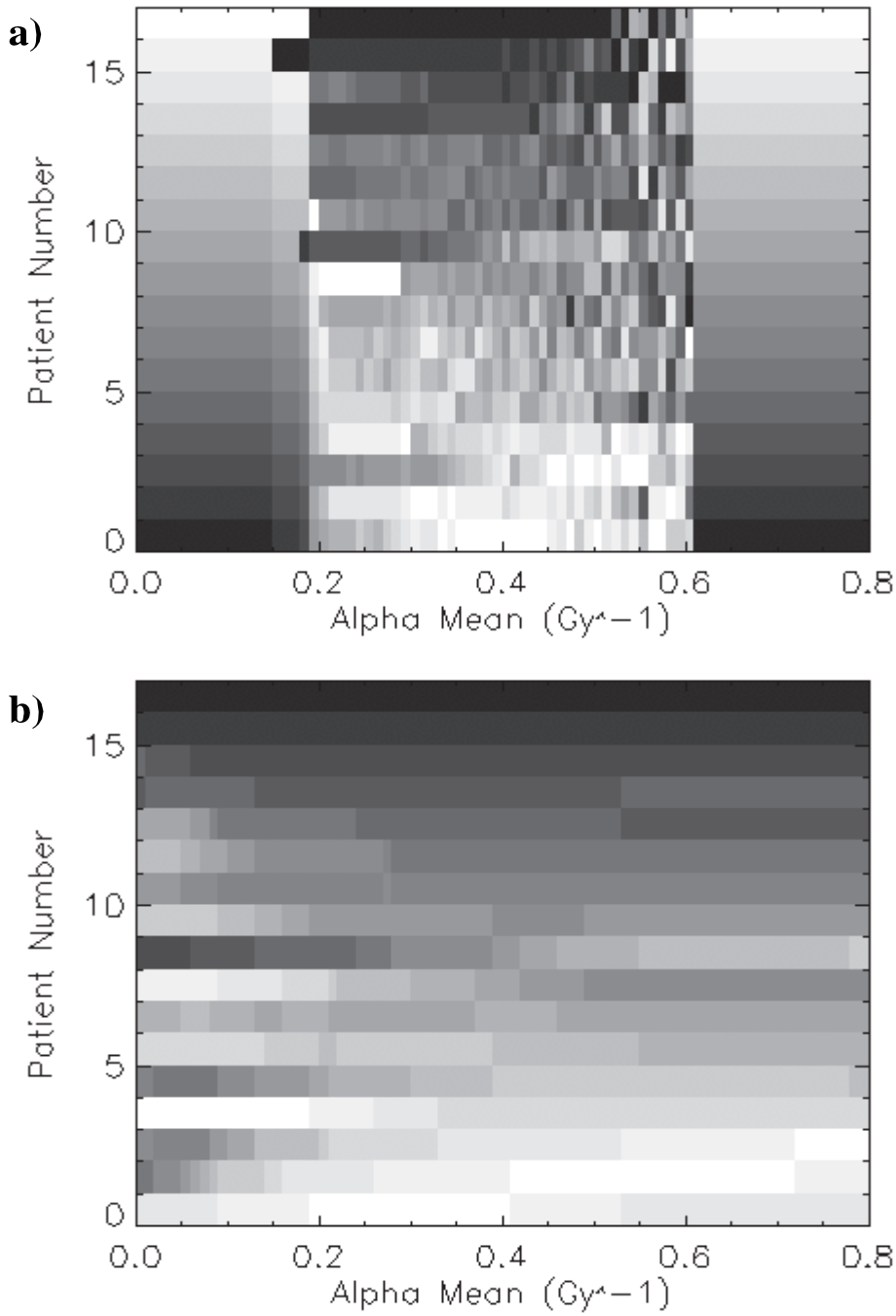

Figure 7. Variation in ranking of the 18 patient DVHs according to a) TCP and b) EUD, and according to the alpha (Gy^{-1}) value used in the TCP/EUD models. Patients have been ranked according to TCP/EUD at $\alpha = 0.4\ Gy^{-1}$. The intensity of the image at each alpha value indicates the ranking of each of the 18 DVHs from lowest TCP/EUD (black) to highest TCP/EUD (white).

Discussion

The results presented above show that if dose-indices are going to be used to rank rival treatment plans, then the resulting ranking is going to depend explicitly on the particular dose-index used. The model DVHs were considered on the basis of the significant differences between them and, as such, it is not surprising that the physical dose-indices give different DVH rankings as shown in Figure 3. What is more surprising is the subtle change in ranking according to EUD as the alpha-parameter was varied (Figure 4b), and the more dramatic change in ranking with TCP as the alpha-parameter was varied (Figure 4a). The change in ranking is also not consistent between TCP and EUD. In Figure 4a the 'underdose' DVH is seen to jump ranking order quite rapidly with change in alpha-value, whereas in Figure 4b it is the 'single-sided Gaussian' distribution which changes ranking most quickly. The strong dependence of TCP on alpha for the underdose DVH is not unexpected as TCP has been shown to be very sensitive to the presence of regions of low dose.[8]

For the data taken from patient PTV dose distributions, there are relatively smaller differences between the 18 DVHs. As a result, smaller but more frequent changes in ranking would be expected. In Figure 5 it is seen that, when the 18 DVHs are ordered according to one of the physical dose-indices, there is considerable variation in the order of the other dose-indices. In Figure 5b, some correlation is seen between minimum and maximum dose and dose standard deviation as may be expected.

In terms of DVH ranking according to the radiobiological dose-indices, Figure 6 shows that there is considerable overlap both for EUD and TCP. This overlap is reflected in Figure 7 as the ranking of individual DVHs (indicated by the intensity of the plot at each combination of patient number and alpha value) changes rapidly with alpha-value indicating a strong sensitivity not only to the radiobiological models, but this parameter of the radiobiological models.

Close examination of Figure 6a a shows some 'noise' in the TCP vs alpha-value curves. This is due to the statistical sampling methods used to incorporate population sampling in the TCP model. Using large values of K in equation (1) leads to significantly long calculation times for TCP and only minimal smoothing of these curves (due to strong effects of low alpha values on TCP). The result is that there will be some overlap of DVH rankings as a result of the sampling routines used and this will lead to some of the rapid variations in ranking displayed in Figure 7.

Conclusions

This study has shown that for a variety of DVH conditions, the ranking of DVHs is dependent on the model used for both physical and radiobiological dose-indices. In addition, the ranking of the DVHs also depends on the particular characteristics of the model being used (in this case, the alpha-value in TCP and EUD models based on the linear-quadratic equation). Variations in the ranking result from non-linear transformations between the indices. This must be considered whenever scalar indices are being used to present dosimetric information in treatment planning, plan optimization or in analysis of dosimetric data from clinical trials.

The usefulness of the variety of available indices for describing non-uniform dose distributions will depend on the correlation of each index with treatment outcome. This information will only become available following detailed assessment of data from large-scale clinical trials.

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