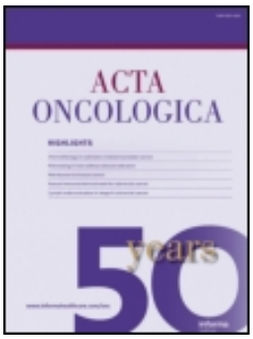

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Behind : In Response to Drs. Mavroidis and Lind

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dose distributions lie at the same position, the corresponding response curves of the organs at risk can be easily compared individually or combined in the total complication response curve, P_I. In this diagram, the confidence intervals of the dose-response curves are also illustrated. It is apparent that the use of the $\bar{\bar{D}}$ concept on the dose axis provides the appropriate dose prescription basis for making such comparisons practical and clinical useful. The normalization using $\bar{\bar{D}}$ gives emphasis to the therapeutic window, which characterizes each treatment plan. Such as the dose volume histogram chart is a good illustration of the volumetric dose distribution delivered to the patient, so is the biological evaluation plot ($P - \bar{\bar{D}}$ diagram) of a dose plan a good illustration of the expected clinical outcome.

Another important clinical use of $\bar{\bar{D}}$ is illustrated in the right diagram of Figure 2. Using a certain set of radiobiological parameters of a given radiobiological model, the dose-response curve of a tissue is calculated for a range of uniform doses. Subsequently, the response probability is calculated for every patient using again those parameters and the individual dose distribution delivered. By applying the concept of biologically effective uniform dose on these probabilities, the corresponding $\bar{\bar{D}}$ values are found. Plotting these dose-response points on the existing diagram they will by definition fall exactly on the theoretical dose-response curve. To examine whether the theoretical curve reproduce the observed response rates it is enough to compare these values for the region around the prescribed dose used by the center where the patients were treated (using a statistical method such as the chi-square test). If the two values are close enough then the parameters can be used for predicting the treatment outcome for the applied technique. This is a simple way to examine if a set of parameters is compatible with the clinical practice that a center uses.

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Behind $\bar{\bar{D}}$: In Response to Drs. Mavroidis and Lind

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To the Editor

We appreciate Drs. Mavroidis and Lind's interest on our short article about the EUD concept [1], and also appreciate their great effort in developing biological measures to evaluate the effectiveness of radiation plans in treating cancer patients [2,3].

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Biologically conformal radiation therapy is the ultimate goal of treating human cancer with radiation, and all various concepts and tools developed to achieve this goal should have great clinical value. In response to Drs. Mavroidis and Lind, we want to share our understanding and comments on the concept "biologically effective uniform dose ($\overline{\overline{D}}$)" and its relation to EUD, as well as other concepts and arguments presented in their letter.

TCP: Binomial distribution vs. Poisson distribution

The Poisson distribution has been widely used in estimating the tumor control probability (TCP). We agree with Mavroidis and Lind that the Poisson statistics may not be accurate for TCP calculation in low dose regions; however, this difference only applies to tumors or tissues with rather flat dose response features. In this letter, we use an example with model parameters similar to those presented by Mavroidis and Lind in their letter and their paper [3] to illustrate this point. Figure 1 shows the TCP curves with different dose response characteristics. While all curves are plotted with a D_{50} (dose to achieve a TCP of 50%) of 80 Gy and a fixed number of fractions, as used by Mavroidis and Lind, the dose response gradient γ at D_{50} is 0.5, 1.0, and 1.5 respectively. The solid curves and dashed curves represent the TCP results with Binomial distribution and Poisson distribution, respectively. As shown in Figure 1, the difference in TCP values between the two models is minimal across the entire dose range when $\gamma = 1$, and it disappears almost completely when $\gamma \geq 1.5$. However, for typical tumor and normal tissues, the dose response is fairly clear and the gradient γ is in the range of 2–4, similar to the example presented by Movroidis et al. (Figure 1 in [3]). Data compiled by Wigg [4] indicate that the mean γ is 2.2 for tumors and 4.3 for normal tissues. The lower γ for tumors is due to tumor heterogeneity. When tumors are stratified by risk factors, the dose response curve becomes steeper, and the γ value approaches 3–4 or even higher [5,6]. Therefore, the Poisson TCP model can provide reliable modeling of the clinical data in the therapeutic dose region, similar to the Binominal statistics [7].

Describing dose response: γ and N_0

As Mavroidis et al. have shown [3], the steepness of the dose response curve is described by parameter γ. For a radiation therapy schedule with a constant dose per fraction, γ is solely determined by the number of clonogen cells of the tumor or the normal tissue functional subunits, N_0,

$$\gamma = \frac{\ln(N_0)}{e}. \quad (1)$$

Mavroidis and Lind used one example to illustrate different concepts. In that example, a gradient $\gamma = 1$ was selected, which is related to a very flat dose response curve as discussed above. The small γ corresponds to a N_0 of only 15, which is a rather low number for tumor clonogens.

The number of clonogen cells in a tumor typically ranges from 10^3 to 10^8 [4,8]. In the studies of the low α/β ratio for prostate cancer, Brenner et al. [9,10] and Fowlor et al. [11] indeed derived a very small N_0 for prostate tumors. However, these modeling studies with such extremely low clonogen numbers were criticized by many other investigators [6,12,13]. In a 2003 study, we analyzed the clinical data collected at MSKCC [5] and derived a N_0 of 1.6×10^6, 3.0×10^6, and 1.1×10^7 for low, intermediate, and high risk patients respectively [6]. These clonogen numbers indicate $\gamma = 5.3$, 5.5, and 6.0 respectively. In a letter to the editor of PMB [14], we mentioned that the relatively flat dose response observed in the clinical data is generally masked by other uncertainties associated with the clinical setting, including patients' risk heterogeneity, dose delivery, outcome definition, and inter-institution variations, etc. Well controlled data from

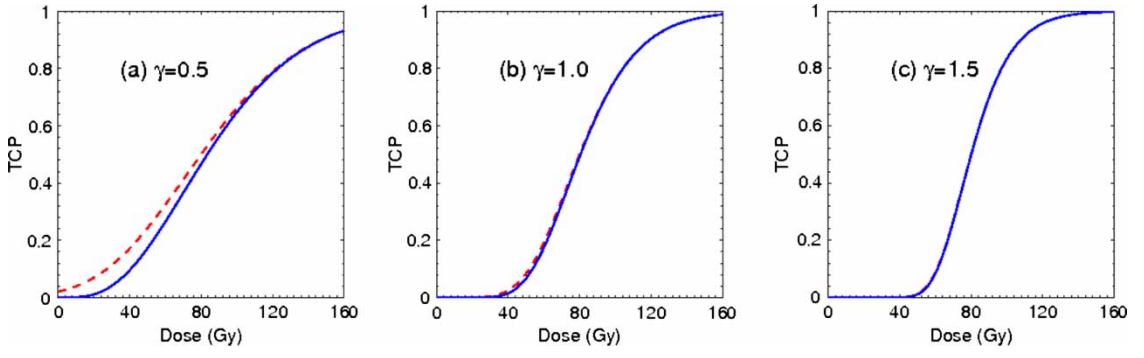

Figure 1. Dose response with two different statistics: Binomial distribution (solid curves) and Poisson distribution (dashed curves). The dose response gradients at D_{50} of 80 Gy are (a) $\gamma = 0.5$, (b) $\gamma = 1.0$, and (c) $\gamma = 1.5$ respectively.

a single institution, if stratified according risk factors, indeed demonstrate steep dose response with a γ value in range of 5–6 [5,6].

As shown above, a low γ value of 1 might be necessary to demonstrate the TCP difference between the Binomial distribution and Poisson distribution, but it is very unusual and is associated with a very flat dose-response curve and an extremely low number of clonogens in a tumor.

Biological equivalence: $\overline{\overline{D}}$ vs. EUD

Both the EUD and the $\overline{\overline{D}}$ have been proposed to illustrate the biological effect of various dose distributions with various radiation delivery schedules/modalities. According to Niemierko [7], EUD is the dose that, when distributed uniformly across the target volume, results in the survival of the same number of clonogens. Similarly, as defined by Mavroidis et al. [3], $\overline{\overline{D}}$ is the uniform dose that results in exactly the same tumor control or normal tissue complication probability as the real dose distribution in a complex target or in the normal tissue of the patient. Based on their definitions, these two concepts are very similar except for the different biological/clinical endpoint used; according to current theory and understanding, the survival of the same number of clonogens/functional subunits in the target will lead to the same control probability if the target is a tumor, or to the same complication probability if the target is a normal tissue.

Mavroidis and Lind investigated the relationship between $\overline{\overline{D}}$ and EUD. In Figure 1 of their letter and Figure 6 in [3], they showed that the two quantities began to diverge from each other at large dose inhomogeneity ($\sigma_D/\overline{D} > 40\%$). We re-plotted the $\overline{\overline{D}}$ and EUD as a function of dose inhomogeneity $\sigma_D/\overline{D}$ in Figure 2; however, we used both the Binomial distribution and the Poisson distribution to calculate EUD (solid curve with Binomial distribution and dashed curve with the Poisson distribution). We found that the EUD curve with Binomial distribution matched the $\overline{\overline{D}}$ curve (triangles overlapped with the solid curve) exactly. Therefore the difference between $\overline{\overline{D}}$ and EUD illustrated by Mavroidis and Lind is actually the difference between Binomial distribution and Poisson distribution. In his initial paper on EUD [7], Niemierko indeed used the Poisson distribution for the EUD derivation, but there is no reason to limit the EUD concept by not using the Binomial distribution for outcome evaluation. When the same statistics are used in TCP calculation, $\overline{\overline{D}}$ and EUD merge into the same concept that describes the biological equivalence of various dose distributions.

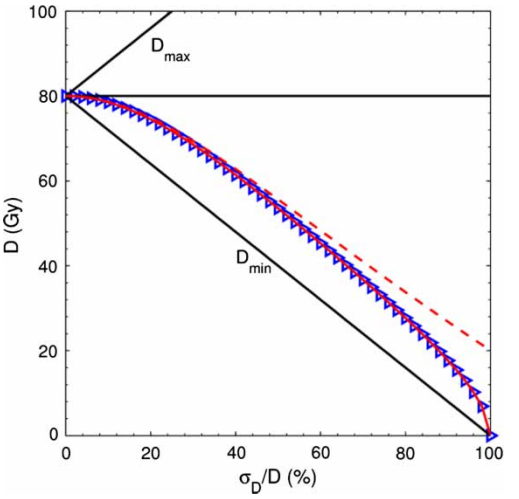

Figure 2. EUD and $\overline{\overline{D}}$ as a function of the dose inhomogeneity $\sigma_D/\overline{D}$. The curves represent the EUD calculations with Binomial distribution (solid curve) and Poisson distribution (dashed curve). The $\overline{\overline{D}}$ calculation is represented by the triangles, which overlap the solid curve.

DVH

Furthermore, we would like to clarify our understanding of the dose-volume histogram (DVH) used in the Mavroidis and Lind's examples (Figure 1 of their letter). According to Mavroidis and Lind, the target is presumed to be divided into two equal parts

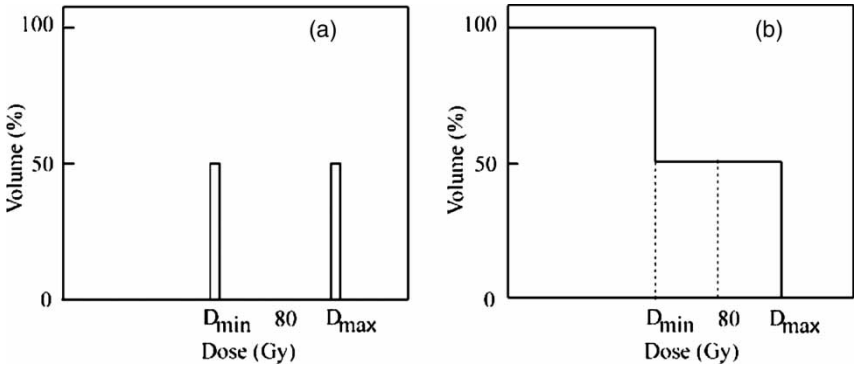

Figure 3. (a) Differential and (b) cumulative dose volume histograms (DVH) used in the example calculation.

that receive a dose of D_{min} or D_{max}. If this is the case, the differential DVH and cumulative DVH should be similar to the DVHs shown in Figure 3, not the left-top DVH plot of Figure 1 shown in Mavroidis and Lind's letter (a similar plot can be found in the Figure 6 in [3]). Here we present Figure 3 to help the reader understand the dose-volume relations used in those examples.

In summary, $\overline{\overline{D}}$ and EUD are the same concept, which is useful to summarize the biological effect of various complex treatment plans. While outcome modeling with Binomial statistics may better estimate the TCP values at low dose regions for cases with a rather flat dose response ($\gamma \leq 1$), Poisson statistics still provide reliable outcome estimates for radiation therapy in the clinical practice.

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Analyzing Toposimerase II-α and HER-2/neu co-amplification seems to be of limited value in epithelial ovarian cancer

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To the Editor

Recurrent chemoresistant ovarian cancer remains a therapeutic challenge; in randomized Phase III trials the best response rates to chemotherapy have been at best 12–13% and even so, short-lived [1,2]. Among available agents, pegylated liposomal doxorubicin is a noteworthy alternative [3]. Pegylated liposomal doxorubicin is, however, quite expensive and has

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