Derivation and representation of dose-volume response from large clinical trial data sets: an example from the RADAR prostate radiotherapy trial

Supplementary Data

ROC-Derivation of Cutpoint
The Youden Index (J) is the point of closest approach to (0,1) on the ROC curve [being a plot, for discrete values of the predictor and a specific event, of (1-specificity) against sensitivity] and approximates the optimal value of the predictor [1, 2] – in this case, a volumetric cut-point. A measure of the discrimination ability of a specific ROC curve is the area under the curve (AUC), being 1.0 for a perfect discriminator and 0.5 for a completely random association. If the observed events are randomly distributed amongst all patients and the resulting AUC of the ROC curve calculated, and this is repeated a large number of times, an approximately normal distribution of AUC values can be derived [3]. If the AUC for the actual patient dataset is compared to this distribution, an estimate of the one-tailed p-value can be obtained [4]. The AUC values required to achieve particular p-values were calculated as a function of the event rate in the population, as shown in Figure 1. This figure also shows the standard deviation of the underlying normal distribution of AUC values, which are centered about AUC = 0.5. It was found that for the range of patients included in analyses as encountered in the RADAR trial, and variety of distributions of volume across most EQD2 intervals, the distributions shown in Figure 2 vary minimally.

Comparison with random data
To evaluate the influence of the underlying DVH data on generated patterns and significance values, the same DVH data used for the examples above were analysed again, with reported grades randomly distributed through the patient population. Two sample resulting plots are shown in Figure 2, displaying limited patterns of dichotomous OR values without significance, and non-significant distributions of J, though which do tend to oscillate about the median range of percentage volume values at each value of EQD2.

Figure 1. ROC curve
AUC values required to achieve a particular one-tailed p-value (as shown for a range of values) against the event proportion (fraction of ‘positives’ in the population of 750 patients in this example). Also shown is the standard deviation of AUC distribution, \( \sigma \), in each case.
Figure 2. Examples of DVH data graphical dose-response assessment for anorectum with toxicity events randomly-allocated to patients in the same proportion to that seen clinically.

1. Schisterman, E.F., et al., *Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples*. Epidemiology, 2005. 16(1): p. 73-81.

2. Zweig, M.H. and G. Campbell, *Receiver operator characteristic (ROC) plots; a fundamental evaluation tool in clinical medicine*. Clin Chem, 1993. 39(5): p. 561-577.

3. Liu, H. and G. Li, *Testing Statistical Significance of the Area under a Receiving Operating Characteristics Curve for Repeated Measures Design with Bootstrapping*. J. Data Science, 2005. 3: p. 257-278.

4. Clark, N.D. and J.A. Granek, *Rank order metrics for quantifying the association of sequence features with gene regulation*. Bioinformatics, 2003. 19(2): p. 212-218.