Supplementary Materials 1

An alternative method of aligning the dose-surface maps

Whether the caudal part of the rectum is particularly sensitive, or whether the observed concentration of a low p-value in this area (Figure 3) depends on the proximity of the prostate, logically associated with a higher dose, is not clear. However, it was found that an anatomical alignment (laterally along the central axis of the OAR, and longitudinally using the ano-rectal junction as origin) discriminated better between patients with and without toxicity, compared to aligning the maps based on isodoses. This suggests that the importance of the caudal area of the rectum is due to a *non-uniform response* in the rectum, rather than the incidental longitudinal location of the isodoses. I.e., if the local dose-response of the OAR were completely uniform spatially, the greatest difference between patients with and without toxicity should have been observed with the maps aligned so that the high doses overlapped the most closely.

An alternative method of unfolding the dose-surface map

In this analysis, the values of the spatial parameters depend on the representation of the ano-rectal wall in 2D. We chose to unfold the DSMs along the posterior axis. Unfolding them along the anterior axis would have instead centred the DSMs on the posterior axis of the rectum, which might have focused the analysis on the pattern of tissue sparing instead of tissue damage. To see which representation best discriminates between the toxicity group and the non-toxicity group, the analysis was repeated with the DSMs unfolded anteriorly (data not shown). For faecal incontinence this representation was worse and no significant pattern was observed for either the anal canal or rectum. However, for rectal bleeding the anterior unfolding of the rectal DSMs was equivalent to the posterior unfolding, in terms of the observed adjusted p-value. The location of the anterior wall is more robust compared to the posterior wall when patient positioning is based on the location of the prostate. Therefore, a greater uncertainty in the dose delivered to the posterior wall can be expected, reducing the detectability of any relevant pattern in tissue sparing.

For rectal bleeding, the significance of both high- and medium doses, and the option to align the DSMs to focus on sparing rather than damage, lends support to the approach used by Munbodh et al. [11], who attempted to represent the limit of cell migration through distance-surface histograms. They found that the area of the rectal wall receiving at least 75 Gy (in 45 fractions), at a distance of 16-22 mm from the 50-Gy isodose was associated with the risk of late rectal bleeding. These parameters were chosen assuming that cell migration from the low-dose region (i.e. less than 50 Gy) to compensate for a high density of tissue damage in the high-dose region can only cover a certain distance.

When applying an anatomical lateral axis, the test-statistic values and p-values were only considered in the central half of the map (although the full map is visualised in Figure 1). If more of the map could have been included, this might have resulted in an even lower p-value for the faecal incontinence analysis. However, it is unlikely that any patterns of interest were undetected since any such differences should have been apparent with the above mentioned analysis with the organ unfolded anteriorly.

DVH characteristics influencing the observed patterns

Figure 5 and Figure 6 below summarize relevant descriptive statistics of the spatial parameters fitted to the data in the study, see Figure 4(A,B) in the manuscript. The standard deviation of each parameter, over the whole cohort included in the study, was calculated, since the variability of a parameter in the dataset may influence the ability to discern a possible association with the

outcome. Further, the cross-correlation between the different isodoses was explored, for each spatial parameter separately. The Spearman correlation coefficient is presented as suggested by El Naqa et al. [43].

The seemingly similar importance of the longitudinal extent of the 13-63 Gy-isodoses for faecal incontinence is probably due to the strong cross-correlation between these parameters in the anal-canal DSMs. For 3D-CRT, late faecal incontinence has been shown to correlate with V_{40} (EQD_2 = 33 Gy, α/β = 3 Gy) [25]. The current study does not contradict that relationship but signals caution regarding the exact isodose; it is expected that for 3D-CRT, cross-correlations between isodoses are at least as predominant compared to IMRT, reducing the robustness of dose-volume predictors.

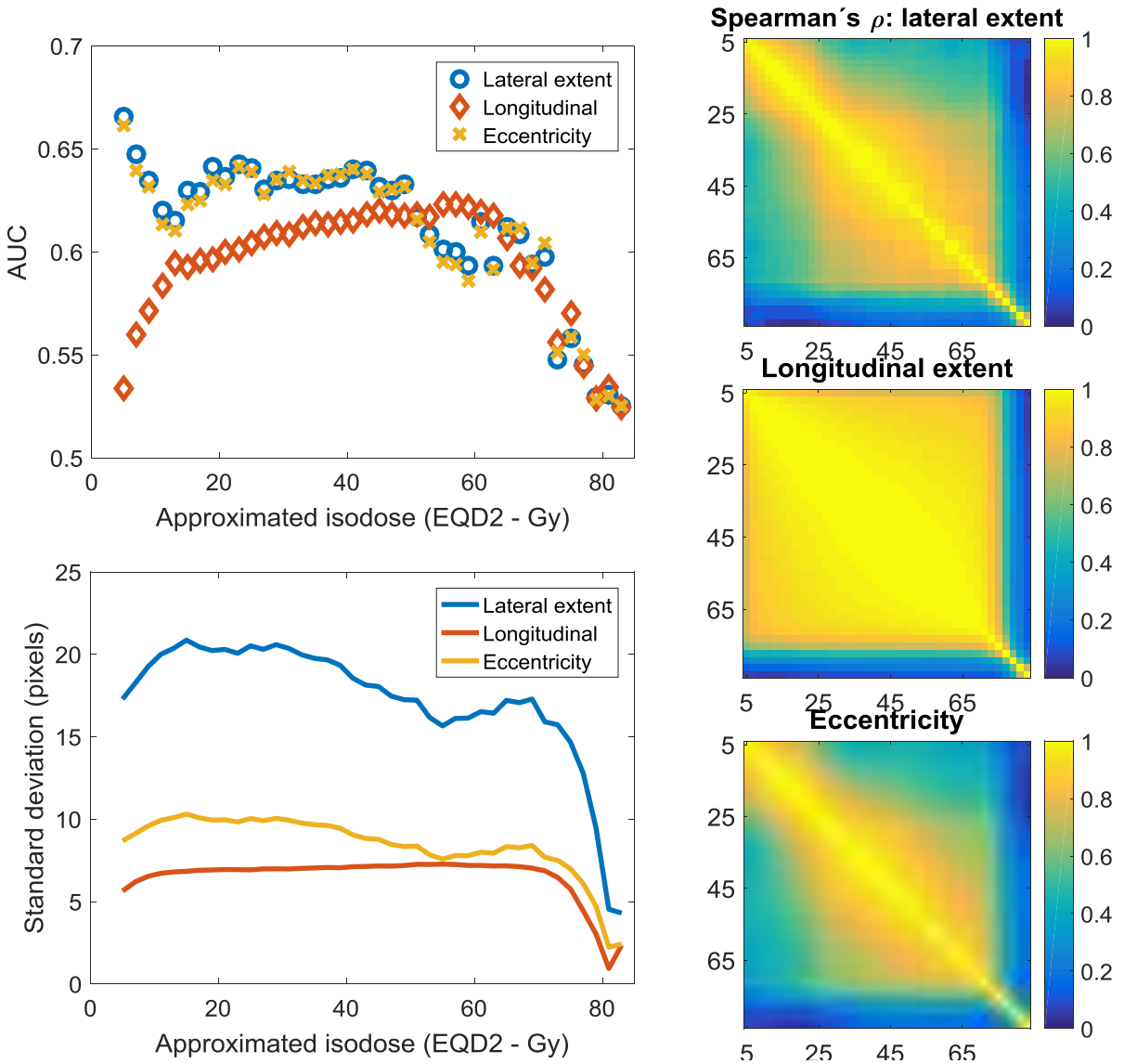

Figure 5. Descriptive statistics for the DSM parameters of the anal canal: on the left, AUC for models fitted to the fecal incontinence outcome data (same as Figure 4(A)) and below the standard deviations of the corresponding parameters, indicating the 'statistical resolution' in the dataset. On the right, Spearman's correlation coefficient for the cross-correlation of each DSM feature (lateral extent, longitudinal extent and eccentricity) over the range of considered isodoses.

A similarly strong cross-correlation was observed in the lateral extent of isodoses in the 45-65-Gy range for the rectum, which may prevent the most important dose level from being highlighted in the analysis of rectal bleeding. Further, the apparent relative importance of the lateral extent of the 31-Gy isodose for rectal bleeding can be explained by a large standard deviation in the current dataset for this particular parameter, rather than by a dose/volume-response mechanism; also, due to cross-correlation, this parameter is likely to be a consistent surrogate of the fraction of rectum included in the volume treated at high dose.

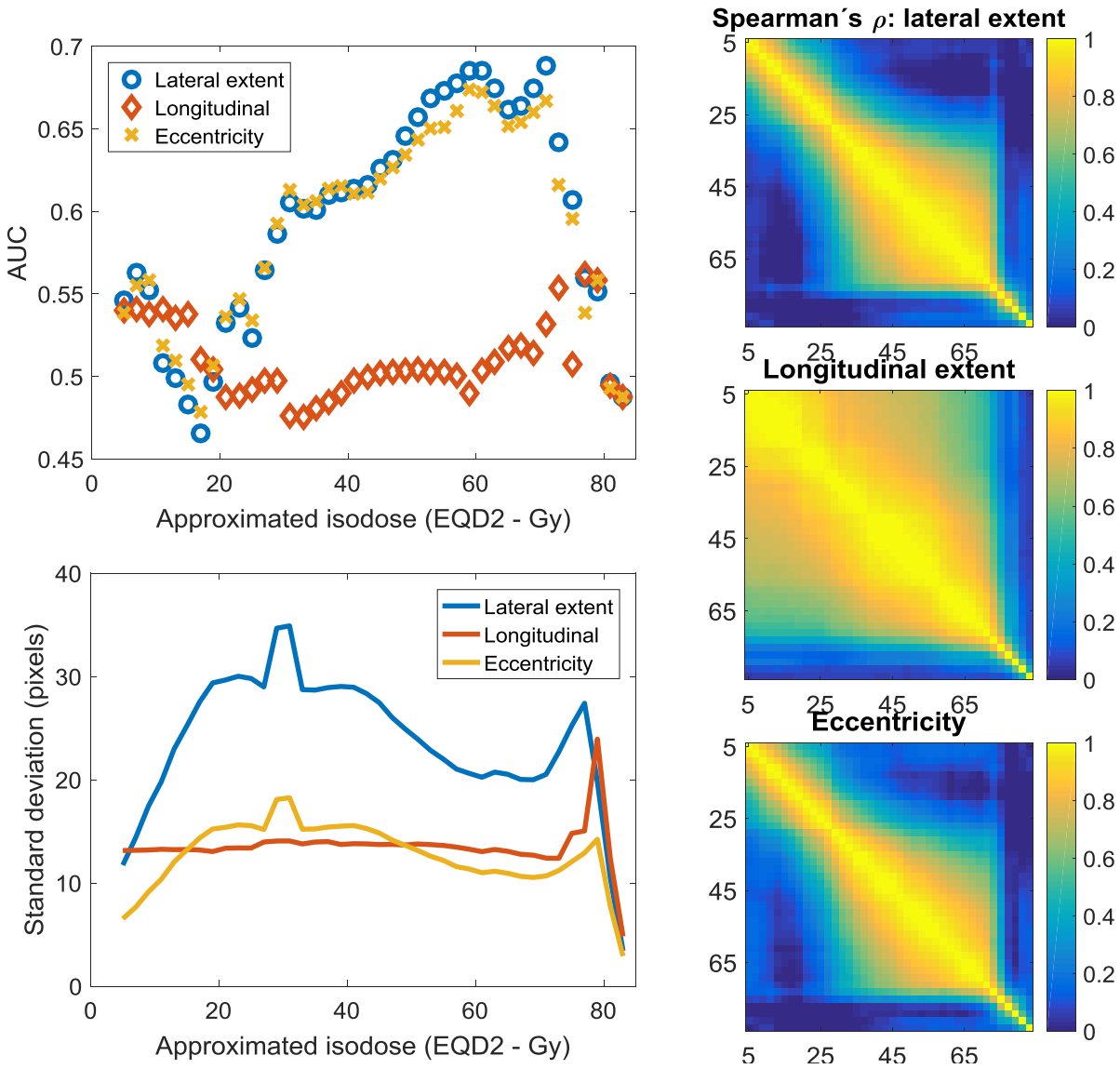

Figure 6. Descriptive statistics for the DSM parameters of the rectum: on the left, AUC for models fitted to the rectal bleeding outcome data (same as Figure 4(B)) and below the standard deviations of the corresponding parameters, indicating the 'statistical resolution' in the dataset. On the right, Spearman's correlation coefficient for the cross-correlation of each DSM feature (lateral extent, longitudinal extent and eccentricity) over the range of considered isodoses.