**SUPPLEMENTARY MATERIAL**

*A. Definition of confidence intervals for AUC values*

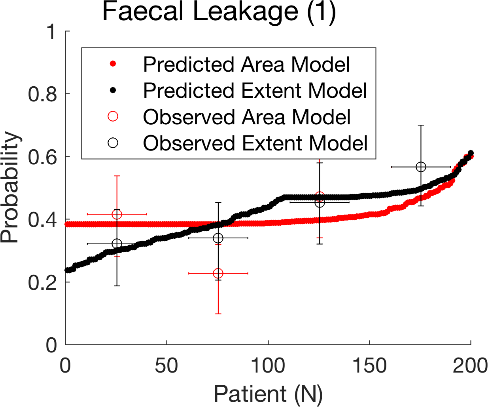
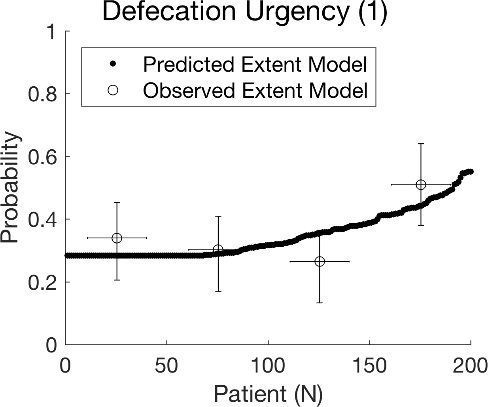
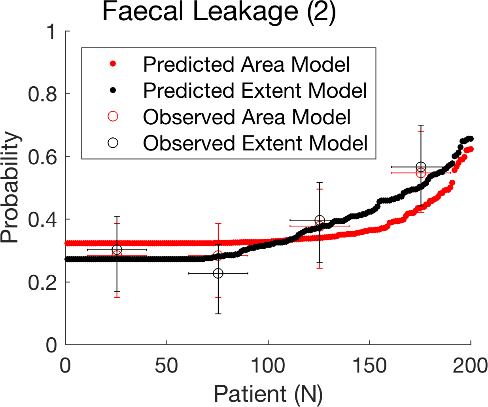
Confidence intervals (CIs) were computed based on the standard error (SE):

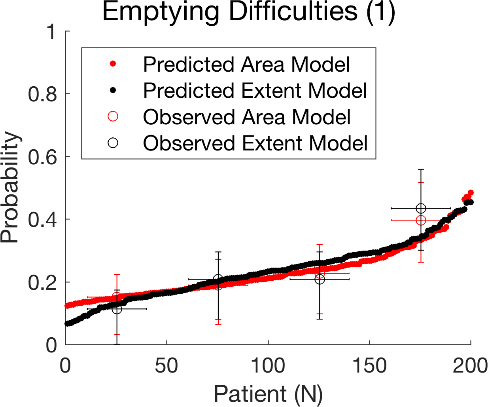
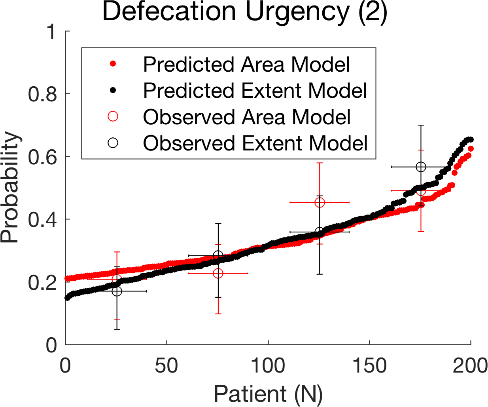
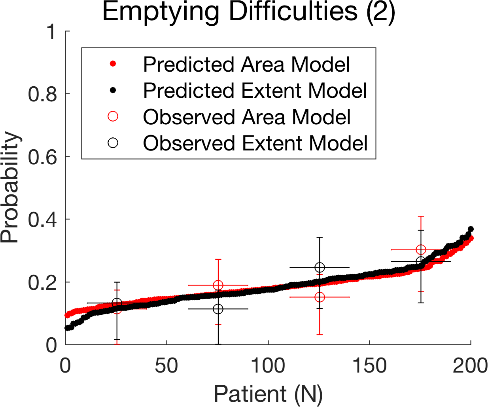
Where *A* is the area under the ROC curve, *na* is the number of events (patients presenting toxicity), where (*na + nn)* gives the total number of patients (Hanley JA, McNeil BJ. Radiology. 1982;143:29-36).

The 95% CI were defined according to:

*B. Dose-response relationship curves*

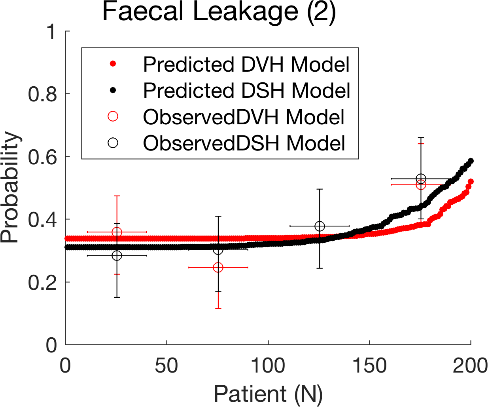
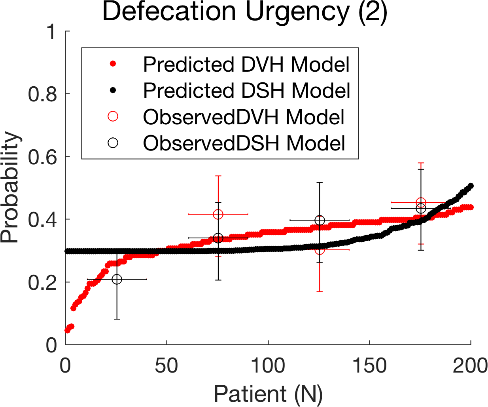
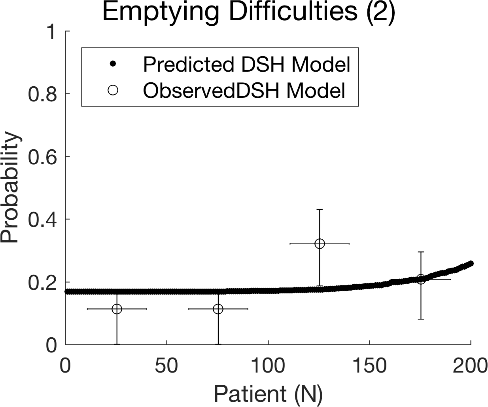
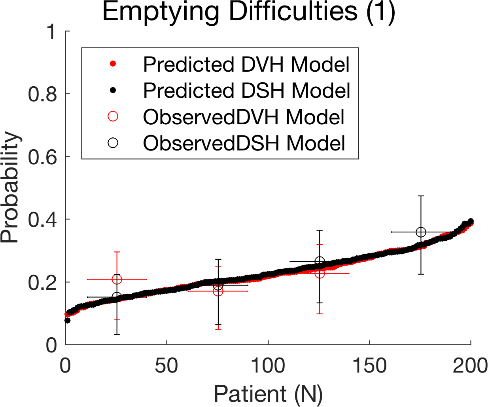
*Spatial-based models*

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*Supplementary Figure 1. Dose response relationship curves and observed toxicity for all the symptoms investigated and for the two map-based approaches (area-based in red, and extent-based in black).*

*DVH/DSH-based models*

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*Supplementary Figure 2. Dose response relationship curves and observed toxicity for all the symptoms investigated and for the two map-based approaches (area-based in red, and extent-based in black). \*Note: only the models that qualified for the MVA are shown.*

C*. Logistic regression coefficients for the final MVA models.*

Dose-response relationships for the metrics in the final MVA models for each symptom follow the logistic regression function:

Where F(x) denotes the predicted probability (black lines in the following figures) for developing a particular symptom, β0 is the intercept of the logistic regression, β1 is the coefficient for metric x1, etc. The cut point responds to the probability of false negative rate at the Youden’s Index of the ROC for the metrics at each model.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Symptom | Symptom  Domain (no) | Question ID | Prevalence  (N) | Metric | B0 | B1/B2 | Cut Point |
| Time to defer  defecation before  toilet visit | **Defecation**  **urgency (1)** | Q7 | 35% (75) | -- | -- | -- | -- |
| Central Lateral 75 Gy Extent | -0.93 | 0.03 | 15% |
| -- | -- | -- | -- |
| -- | -- | -- | -- |
| Immediate toilet visit due to urgency | **Defecation**  **urgency (2)** | Q23 | 34% (73) | Upper Left 60 Gy Area  Left 70 Gy Area | -1.32 | 0.03/0.06 | 6%/5% |
| Lateral Central 75 Gy Extent  Lateral Upper 50 Gy Extent | -1.83 | 0.03/0.03 | 7%/27% |
| D10 | -0.12 | 0.17 | 1% |
| A60 | -0.86 | 0.05 | 3% |
| Involuntary  gas discharge | **Faecal**  **leakage (1)** | Q1 | 42% (89) | Central Anterior 75 Gy Area | -0.48 | 0.02 | 1% |
| Lateral Central 75 Gy Extent  Lateral Central 45 Gy Extent | -2.38 | 0.04/0.02 | 1%/99% |
| -- | -- | -- | -- |
| -- | -- | -- | -- |
| Soiling of underwear  after toilet visit | **Faecal**  **leakage (2)** | Q8 | 37% (79) | Central Anterior 75 Gy Area | -0.74 | 0.03 | 2% |
| Lateral Central 75 Gy Extent | -0.99 | 0.04 | 5% |
| V75 | -0.67 | 0.31 |  |
| A60 | -0.79 | 0.06 |  |
| Incomplete evacuation  of stools | **Emptying Difficulties (1)** | Q12 | 24% (51) | Upper Left 65 Gy Area  Lower 50 Gy Area | -2.07 | 0.04/0.02 | 14%/13% |
| Longitudinal 45 Gy Extent  Upper Lateral 75 Gy Extent | -4.27 | 0.03/0.02 | 75%/34% |
| V50 | -2.75 | 0.04 |  |
| A35 | -3.74 | 0.04 |  |
| Need to strain  when defecating | **Emptying Difficulties (2)** | Q17 | 19% (40) | Central Right 50Gy Area | -2.47 | 0.02 | 49% |
| Lateral Central 55 Gy Extent  Longitudinal Right 60 Gy Extent | -4.15 | 0.02/0.03 | 65%/55% |
| -- | -- | -- | -- |
| A60 | -1.59 | 0.03 |  |

*D. Permutation analysis*

The plots below are the results from the permutation analysis of all seven symptoms, in the left panel of each figure the normalized difference map is showed, this map is generated as the ratio between the averaged difference map and the standard deviation map. In the middle panel the histogram for the maximum observed difference for each permutation is shown where the red solid vertical line indicates the adjusted p-value for each particular endpoint. The right panel gives the averaged difference 2D maps (ΔDSM) where the white contours enclose differences at the 5% and black contours differences at the 10% significance level.

*E. Rectum Statistics*

For completeness we computed mean and standard deviation of the rectum volume, rectum length and rectum cross sectional area.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Rectum Volume | Rectum Length | Cross Sectional Area |
| Mean ± SD | 92.6 ± 41.9 cm3 | 9.0 ± 3.7 cm | 11.8 ± 6.9 cm2 |