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FULL PAPER

Accumulated dose to the rectum, measured using dose-volume histograms and dose-surface maps, is different from planned dose in all patients treated with radiotherapy for prostate cancer

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Objective: We sought to calculate accumulated dose (D_A) to the rectum in patients treated with radiotherapy for prostate cancer. We were particularly interested in whether dose-surface maps (DSMs) provide additional information to dose-volume histograms (DVHs).

Methods: Manual rectal contours were obtained for kilovoltage and daily megavoltage CT scans for 10 participants from the VoxTox study (380 scans). Daily delivered dose recalculation was performed using a ray-tracing algorithm. Delivered DVHs were summated to create accumulated DVHs. The rectum was considered as a cylinder, cut and unfolded to produce daily delivered DSMs; these were summated to produce accumulated DSMs.

Results: Accumulated dose-volumes were different from planned in all participants. For one participant, all D_A levels were higher and all volumes were larger than

planned. For four participants, all D_A levels were lower and all volumes were smaller than planned. For each of these four participants, $\geq 1\%$ of pixels on the accumulated DSM received ≥ 5 Gy more than had been planned.

Conclusion: Differences between accumulated and planned dose-volumes were seen in all participants. DSMs were able to identify differences between D_A and planned dose that could not be appreciated from the DVHs. Further work is needed to extract the dose data embedded in the DSMs. These will be correlated with toxicity as part of the VoxTox Programme.

Advances in knowledge: DSMs are able to identify differences between D_A and planned dose that cannot be appreciated from DVHs alone and should be incorporated into future studies investigating links between D_A and toxicity.

INTRODUCTION

Prostate cancer is the most common cancer affecting males in the UK, accounting for 26% of all new cases of cancer in males in England in 2012.¹ Overall survival measured at 10 years from diagnosis is the fourth highest of all cancers in the UK at 84%.^{2,3} External beam radiotherapy (RT) is one of several treatment options available to patients with non-metastatic disease.⁴ The introduction of three-dimensional (3D) conformal RT in the 1990s reduced toxicity and so enabled dose escalation to the prostate; this translated into improved tumour

control as measured by biochemical progression in various clinical trials.⁵⁻⁹ This was, however, at the expense of increased \geq grade 2 late gastrointestinal toxicity, seen in each trial.⁷⁻¹¹

Since this time, development of other technologies, such as intensity modulation and image guidance, has enabled the dose to normal tissues to be reduced, with consequent improvements in toxicity.¹²⁻¹⁷ Advances in dose computation offer the potential to reduce the dose to normal tissues even further, by adapting the dose distribution

during treatment on an individual basis. If the dose could be reduced to critical structures then there may be opportunity for further dose escalation to tumour. Methods to estimate this may identify a subgroup of patients in whom safe dose escalation could be undertaken. These approaches are likely to have application in prostate cancer given the positional variation of the rectum during treatment, its proximity to the tumour target and the use of hypo-fractionated schedules.^{18–27}

In order to be able to accurately predict normal tissue complication probability (NTCP) in an individual, understanding the precise relationship between dose and toxicity is essential. At present, predictive models are based on “planned” dose–volume histograms (DVHs) calculated from a single planning CT scan before treatment.²⁸ This does not incorporate any measure of anatomic variation during treatment, which has been shown to affect dose to the rectum in several studies.^{19,23,24,29–31} In addition, DVHs as produced from the treatment plan are not ideal representations of 3D doses as they discard spatial information.²⁸

To our knowledge, four studies in the literature have used daily image guidance CT scans to calculate accumulated dose (D_A) to the rectum over a course of RT for prostate cancer.^{23,24,30,31} Two used helical tomotherapy megavoltage (MV) scans, one used CT-on-rails and one used MV cone-beam CT. Whilst providing useful early data, each of these studies was limited by one or more factors. These included: missing scans (unable to be retrieved), poor quality scans (in some cases the prostate was not scanned and in some there were unacceptable artefacts), inadequacy of imaged rectal volumes, inspection of only one or two dose-volume levels, and deforming planned dose distributions onto new anatomy, rather than recalculating the dose. We sought to improve on these, by recalculating dose on daily scans from patients treated with RT to prostate and pelvic lymph nodes, and summing these data to produce accumulated DVHs. We also developed dose–surface maps (DSMs) as a way of retaining 3D dose information. These measures of D_A will be correlated with toxicity as part of the VoxTox study.³²

METHODS AND MATERIALS

Ethics approval for the VoxTox study was granted on 4 February 2013. This is an observational study to collect comprehensive toxicity data for 1500 patients undergoing image-guided intensity-modulated radiotherapy (IMRT) to the prostate, head and neck and central nervous system. The aim is to establish the toxicity following treatment and how this relates to the D_A to the rectum, salivary glands and hypothalamic–pituitary axis.

Rectal contours for 10 study participants were obtained as previously described.¹⁸ Each participant was treated using helical tomotherapy, with intensity modulation and daily MV image guidance and positional correction to a dose of 74 Gy in 37 fractions over 7.5 weeks.³³ Following training with a radiologist, JES outlined the rectum on the kilovoltage (kV) planning scan and daily MV image guidance scans for the 10 participants using ProSoma® (Oncology Systems Limited, Shropshire, UK). The entire circumference of the rectal wall was contoured on each slice of each MV scan where it was shown. Digital imaging and

communications in medicine (DICOM) RT plans, and the translational and rotational setup errors (X, Y, Z and roll) identified by the radiographers for each fraction, were retrieved from the TomoTherapy® (Accuray, Sunnyvale, CA) archive using in-house software.³⁴ All data were anonymized and tokenized and then transferred from the hospital network to the University Physics Laboratory for storage, curation and processing.

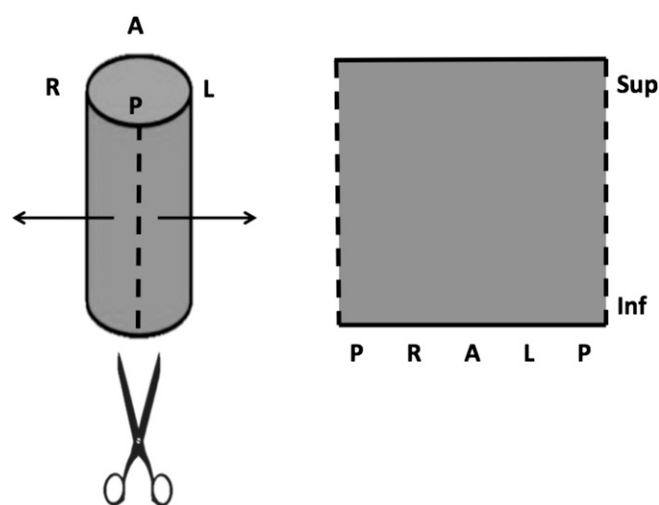
Analysis of the MV CT scans revealed that the external contour of the body laterally was not shown in some cases. This was due to the scan circle of the MV CT being 38.6 cm diameter, and too small to encompass the entire patient outline. To address this, the relevant daily shift was applied to the centre of the MV CT, and the corresponding part of the kV image was used for any tissue falling outside the circle. A masked kV image was created by setting all Hounsfield unit (HU) values within the circle to -1000 (corresponding to zero density), and merged with the MV CT. The superior rectum was present on all MV scans; in cases where the MV scan did not extend sufficiently to show the inferior rectum, contours and slices from the kV scan were used.¹⁸

A dose calculation programme was written as a command-line application in MATLAB® (MathWorks®, Natick, MA). This performed a ray-tracing algorithm over a set of points covering the image.³⁵ Dose calculations were carried out at each point, using a radiological path length calculated as the sum of those for the MVCT image and for the masked kV image. The use of a separate masked image, rather than one composite image, took account of differences in pixel spacing and HU to electron density conversions between the scans. For MV scans, the HU to electron density conversion varied slightly with the date of image acquisition. We have measured this using a “cheese phantom” with density inserts as part of the monthly quality assurance checks over a seven-year period. The appropriate conversion was used for each MV scan; this depended on the date of the scan and which of our two TomoTherapy machines was used. The calculated dose cube was saved as a DICOM RT dose object. The superior rectum was present on all MV scans; in cases where the MV scan did not extend sufficiently to show the inferior rectum, contours and slices from the kV scan were used.¹⁸

Daily “delivered” DVHs were produced for each participant; these were summated to produce “accumulated” DVHs. Volumes of rectum receiving 20, 30, 40, 50, 60, 65, 70 and 75 Gy, and doses to 80%, 70%, 65%, 60%, 55%, 50%, 40%, 30%, 25%, 15%, 5% and 3% of the rectum, were compared with those planned. Accumulated generalized equivalent uniform doses (gEUDs) were calculated using $a = 11.11$ as per quantitative analyses of normal tissue effects in the clinic (QUANTEC).³⁶ The doses and volumes chosen comprised the constraints from two recent trials.^{37,38}

Planned and daily delivered DSMs were produced based on algorithms described by Murray et al.³⁹ and Buettner et al.⁴⁰ The rectum was considered as a cylinder and dose was sampled at points on each CT slice. The cylinder was “cut” at the point where a vertical line from the centroid of each contour crossed the posterior edge and unfolded (Figure 1).

Figure 1. Graphical illustration of the rectum as a cylinder. The cylinder was “cut” at the point where a vertical line from the centroid of each contour crossed the posterior edge, and unfolded.



Each pixel on a DSM comprised a horizontal (posterior–posterior) coordinate and a vertical (superior–inferior) coordinate, with the doses at these points displayed. To obtain the horizontal coordinates, the rectal circumference was measured on the outline for each CT slice and divided by 20. Coordinates were then determined as 21 equally spaced points around the circumference with the first and 21st being at the cut point. For the vertical coordinates, we used the longitudinal coordinates of the kV CT slices. The dose at each of these points was then determined by interpolation into the calculated dose matrix.

Accumulated DSMs were constructed by summing the pixels from the delivered DSMs. For participants where the inferior rectum was not shown on any MV scans, this part of the accumulated DSM appeared identical to the planned DSM. To avoid this, in Figures 2 and 3 we have greyed out all slices where

none of the MV slices extended sufficiently. Each pixel from the planned DSM was then subtracted from the equivalent pixel from the accumulated DSM to produce a “difference” DSM for each participant. These were inspected to assess whether they provided additional information above that from the DVHs.

To facilitate visual comparison of the DSMs, we developed a system to standardize their superior–inferior lengths. The median MV radius during treatment was calculated for each participant as previously described.¹⁸ The mean of this value and the corresponding kV radius was used to calculate a rectal circumference for each participant. The circumference was then divided into 20 equal parts, each corresponding to the width of a square pixel on the DSM. For each participant, the superior–inferior kV rectal length was divided by the pixel size. The median of the results for the 10 participants was used as the superior–inferior length of the DSMs.

RESULTS

The accumulated gEUD was different from the planned gEUD in all 10 participants (median -2.7 Gy, range -10.2 to $+5.3$ Gy), and lower in 7 of the 10; full results are shown in Table 1. DVHs for the participant with the highest accumulated compared with planned gEUD (Participant A) are shown in Figure 4; DVHs for the participant with the lowest accumulated compared with planned gEUD (Participant B) are also shown (Figure 4). The median relative accumulated gEUD for the 10 participants was 95% of planned (range 83–109%).

Differences between accumulated and planned dose to particular volumes of the rectum for the 10 participants are illustrated in Figure 5. Differences in the volumes receiving particular doses are also shown. For one participant (A), all D_{AS} and volumes were higher than planned. For four participants (B–E), all D_{AS} and volumes were lower than planned. For one participant (F), all D_{AS} and volumes were lower or the same as planned. For the remaining four participants, some D_{AS} and volumes were higher and some lower than planned. Planned, accumulated and difference DSMs for Participant A are shown in Figure 2.

Figure 2. Planned dose–surface map (DSM) and accumulated DSM for Participant A. The difference DSM is also shown, where each pixel from the planned DSM has been subtracted from the equivalent pixel from the accumulated DSM. The dose colour scale for planned and accumulated DSMs is shown on the left and for the difference DSM is shown on the right. Differences in dose of up to $+18.2$ Gy were seen, particularly to the posterior rectal wall. Where none of the megavoltage scans extended sufficiently inferior, the relevant slices of rectum have been greyed out. A, anterior; Gy, Gray; Inf, inferior; L, left; P, posterior; R, right; Sup, superior.

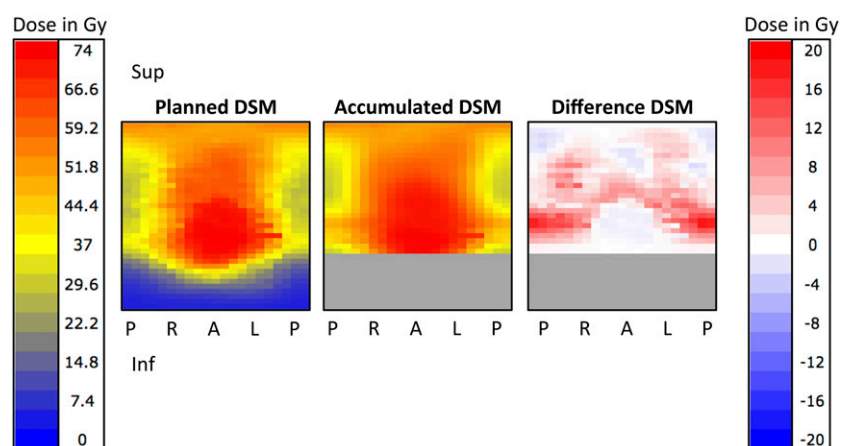
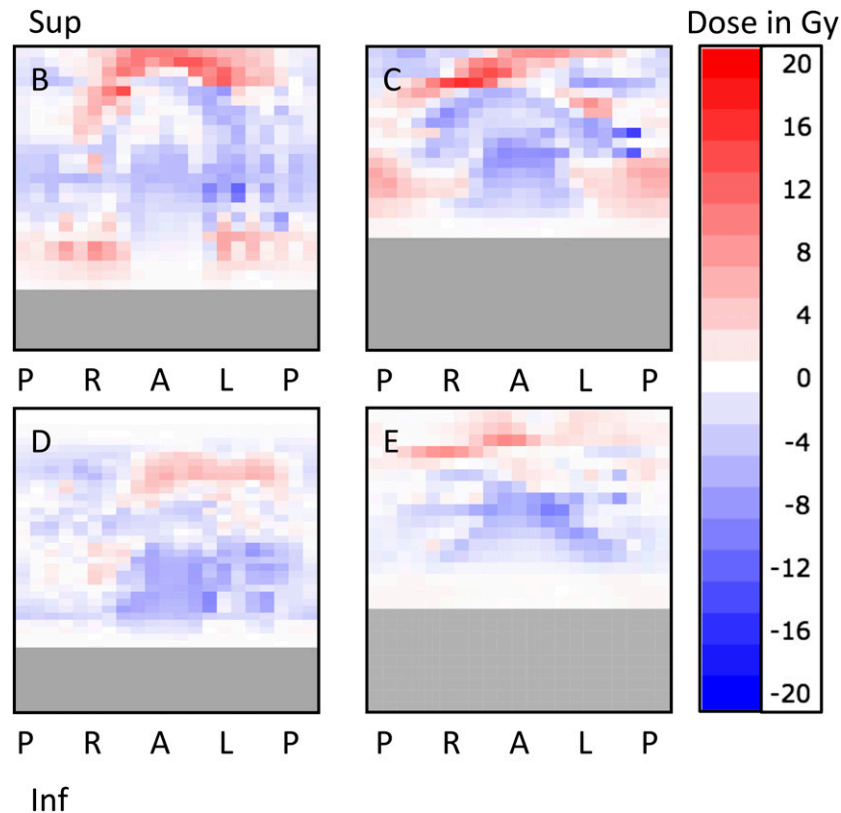


Figure 3. Difference dose–surface maps (DSMs) for Participants B–E. In all four, some pixels received higher accumulated dose (D_A) than planned, despite their dose–volume histograms showing lower D_A s and volumes. The percentage of pixels receiving higher D_A ranged from 27% (D) to 48% (E). The percentage of pixels receiving ≥ 5 Gy higher dose than planned ranged from 1% (D) to 12% (C). Where none of the megavoltage scans extended sufficiently inferior, the relevant slices of rectum have been greyed out. A, anterior; Gy, Gray; Inf, inferior; L, left; P, posterior; R, right; Sup, superior.



Difference DSMs for Participants B–E are shown in Figure 3. In all four cases, some pixels received higher accumulated than planned dose, despite DVHs showing that D_A s and volumes were lower than planned. The percentage of pixels receiving higher accumulated than planned dose ranged from 27% (D) to 48% (E). The percentage of pixels receiving ≥ 5 Gy higher accumulated than planned dose ranged from 1% (D) to 12% (C).

DISCUSSION

Late rectal toxicity occurs ≥ 90 days after RT and may include bleeding, mucous, urgency, frequent loose bowel movements, pain and incontinence.³⁶ These morbidities can be severe and markedly affect the quality of life.³⁶ The cumulative incidence of \geq grade 2 toxicity, using the Radiation Therapy Oncology Group (RTOG) scale, in the dose escalated arm of major randomized trials using conformal RT, has been reported as between 18% and 35% with a minimum median follow up of 5.3 years.^{7,8,10,11,41} With IMRT, rates have been reported as between 6% and 26% with a minimum median follow up of 2.4 years.^{13–15,27} Although these data have yet to mature, they indicate that serious toxicity can affect appreciable numbers of males.

Published DVH thresholds for toxicity of RTOG \geq grade 2 converge at doses >70 Gy, and volumes $<20\%$, suggesting that these values are more consistently associated with toxicity.³⁶ Five separate fits of the Lyman–Kutcher–Burman NTCP model to rectal toxicity data

have estimated similar parameters.^{42–46} The volume effect parameter tended to be small (<0.15), implying serial architecture, with high-dose regions playing the predominant role in determining toxicity risk.³⁶ However, other work suggests that volumes receiving lower doses might also be contributory; a constraint for incontinence of $V_{40\text{Gy}} < 65\text{--}70\%$ has been suggested, for example.^{37,47–51} This may be due to the volumes exposed to intermediate doses playing a role in the recovery of tissue exposed to high doses.⁵² Analysis of the RT01 trial has shown that the number of DVH constraint points which are violated, and the shape of the dose distribution, are correlated with outcome.^{51,53}

These models use sample population data to predict the NTCP for an individual based on their RT plan. If a group of patients representative of the underlying population with identical plans was investigated, the median toxicity expressed by the group would be likely to reflect the NTCP. It is highly unlikely that the toxicity expressed by each individual patient would be identical. This is partly explained by variation in intrinsic patient factors reported to influence late toxicity such as diabetes, haemorrhoids, inflammatory bowel disease, advanced age, androgen deprivation therapy, rectum size, prior abdominal surgery and severe acute rectal toxicity.³⁶ There is also likely to be a genetic component to the variation; this is an area of active research.^{54–56} The third factor to consider is the difference between the planned DVH and what was actually delivered. This is crucial, as there is

Table 1. Comparison of planned and accumulated dose (D_A) for the 10 participants using generalized equivalent uniform dose (gEUD). Dose differences (accumulated gEUD minus planned gEUD) are also shown

Participant	gEUD (Gy)		
	Planned	Accumulated	Difference
A	56.9	62.2	5.3
B	60.3	50.1	-10.2
C	58.8	55.8	-3.0
D	53.3	47.3	-6.0
E	57.1	50.2	-6.9
F	57.3	53.8	-3.6
G	60.3	61.3	1.1
H	56.4	55.0	-1.4
I	56.0	53.6	-2.4
J	60.8	61.1	0.3
		Mean	-2.7
		Median	-2.7

potential for monitoring delivered dose during treatment, and for treatment adaptation if required. Minimizing variation in physical dose would also contribute to greater understanding of the role of intrinsic and genetic factors.

In line with the theory that the median toxicity expressed by a group of patients with identical RT plans would equal that predicted, we have shown that for our group of 10 patients, the median position of the axial centre of the rectum over the 370 treatment fractions was within 1 mm of its position at RT planning.¹⁸ This suggests that at the population level, the RT plan is a good surrogate for D_A . However, considering the participants individually, we found differences between accumulated and planned gEUDs in all 10 cases. 1/10 had higher accumulated than planned gEUD, in 6/10 cases accumulated gEUD was lower than planned and in 3/10 the gEUDs were within 1 Gy of each other. In a group of 8 patients, Akino et al found similar results, with higher accumulated than planned gEUD in 1/8, lower in 6/8 and 1/8 within 1 Gy.³¹

Consistent with this, we also found differences between accumulated and planned DVHs for each of our 10 patients. Accumulated $V_{70\text{Gy}}$ was higher than planned in one participant (A) and lower by >2% in three participants (B, C and E) as shown in Figure 5. Results were within 2% for the remaining six participants. This is in contrast to previous work by Hatton et al,²⁹ where 7/12 patients had higher accumulated $V_{70\text{Gy}}$ than planned, 3/12 were lower and two were similar. This difference may be due to the frequency of their CT scans being twice a week, rather than daily, and also to their use of cone-beam CT, which may be associated with dose recalculation errors due to uncertainties in the HU values.²⁹ 3 out of our 10 participants (30%) had accumulated $V_{65\text{Gy}} > 17\%$; this is similar to the rate of 27% of scans seen in a study by Chen et al.¹⁹ Accumulated $D_{3\%}$ was higher than planned in one participant (A) and

Figure 4. Dose-volume histograms (DVHs) for Participants A and B. The original planned DVHs for both participants were very similar, with planned generalized equivalent uniform dose (gEUD) of 56.9 Gy for A and 60.3 Gy for B. However, the accumulated gEUD for A was 62.2 Gy (5.3 Gy greater than planned) and for B was 50.1 Gy (10.2 Gy less than planned).

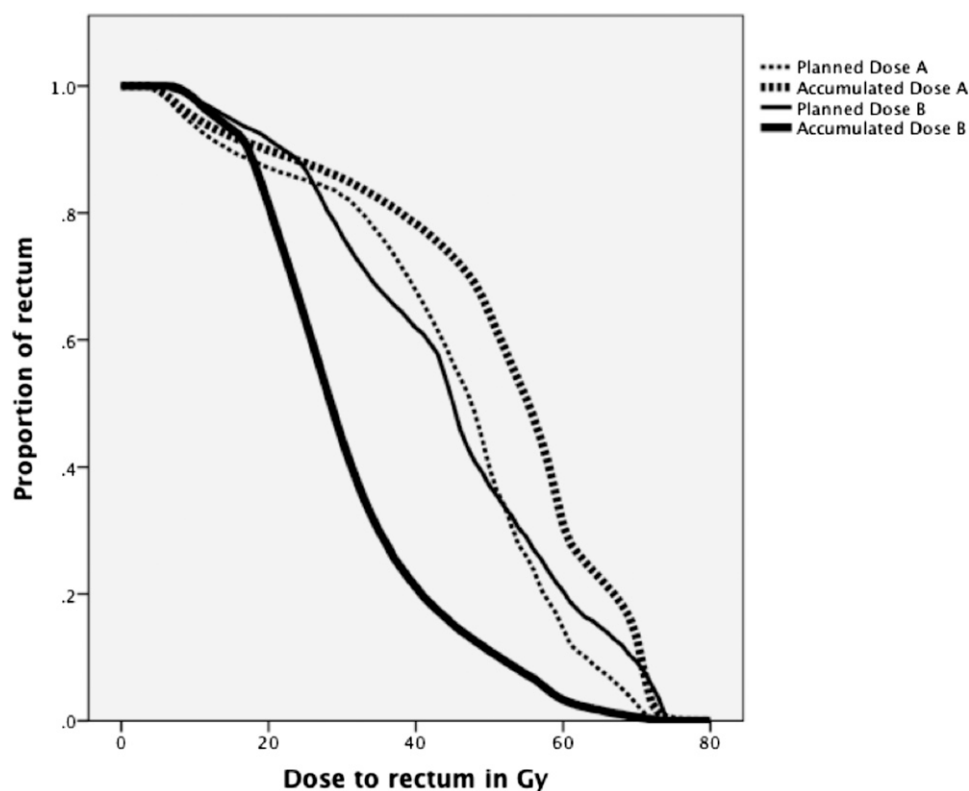
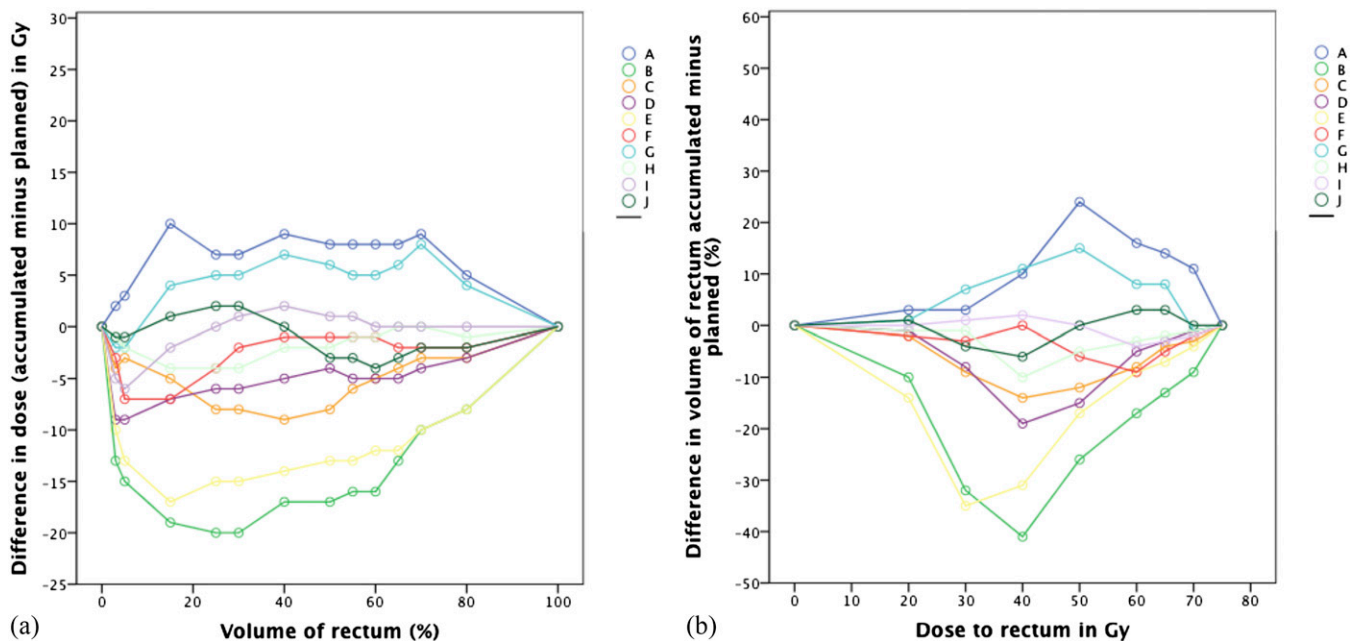


Figure 5. Graphs showing absolute differences in dose (a) and volumes of rectum (b) between accumulated and planned dose-volume histograms (DVHs) for the 10 participants. Doses to 80%, 70%, 65%, 60%, 55%, 50%, 40%, 30%, 25%, 15%, 5% and 3% of the rectum are shown in (a) and volumes treated to 20, 30, 40, 50, 60, 65, 70 and 75 Gy are shown in (b). For Participant A, all accumulated doses and volumes were higher than planned. For Participants B–E, these were all lower than planned.



lower by $>2\%$ in 6/10 participants as shown in Figure 5. In Akino's study, 0/8 patients had higher accumulated $D_{2\%}$ and it was lower by $>2\%$ in 5/8; these are similar to our results.³¹

The most extreme differences in accumulated $V_{70\text{Gy}}$ were for Participants A and B. Accumulated $V_{70\text{Gy}}$ for Participant A was 13%, whereas the planned $V_{70\text{Gy}}$ had been only 3%. For Participant B the reverse was seen; accumulated $V_{70\text{Gy}}$ was 1%, whereas it was 9% at planning. As doses above this level are more consistently associated with toxicity, we anticipate that Participant A would be more likely to express toxicity than suggested by their NTCP, and that Participant B would be less likely to. If volumes receiving lower doses are also contributory then perhaps Participant G, who received a $V_{40\text{Gy}}$ of 73% when 62% had been planned, might be more likely to display toxicity than suggested by his NTCP. The converse would be true for Participant E: planned $V_{40\text{Gy}}$ had been 48%, whereas actually the accumulated $V_{40\text{Gy}}$ was 17%.

Summated DVHs suffer from a number of limitations when considering D_A . Even when the DVHs on 2 days show the same volume receiving a given dose, the lack of spatial information in a DVH means that these may correspond to different parts of the rectum, meaning that these do not necessarily correspond to a true D_A DVH. Secondly, a DVH also cannot distinguish between the rectal wall and the rectal contents. The use of rectal wall DSMs, which preserve spatial information, avoids both these problems.

We have successfully implemented a method to generate planned, accumulated and difference DSMs. By "cutting" the surface at a point posterior of the centroid of each image, we ensured that the central column of the DSM corresponded to the middle of the

anterior surface of the rectum. This is in contrast to the splitting at the most posterior point of each outline as described by Murray et al, which we found led to large variations from slice to slice. All 10 participants had pixels on the difference DSM that were $>+2\text{ Gy}$; these tended to be located superiorly and posteriorly. This is not surprising, as these areas are away from the prostate, the region where set-up is verified and is consistent with findings from Murray et al.³⁹ All 10 participants also had pixels on the difference DSM that were $<2\text{ Gy}$; these tended to affect the anterior rectum. Further work is needed to extract the dose data embedded in the DSMs; approaches that may be relevant include mapping of dose to height and width parameters, eccentricity of higher dose regions and regularity of isodose contours.^{53,57}

Previous work with planned DSMs found that the risk of rectal bleeding was higher for patients in whom $>37.4\%$ of the pixels received at least 51 Gy.⁵³ None of our 10 participants exceeded this threshold on the planned DSM; 2, however, did exceed it on the accumulated DSM (A and J). Although this parameter could have been predicted from the accumulated DVH for Participant A, it would not have been detected for J (Figure 5). Increased bleeding risk has also been found where the lateral extent of the 61 Gy isodose exceeded 59% of the circumference of the rectum.⁵³ This was the case for 4/10 of our Participants, A, E, F and J, and applied to both planned and accumulated DSMs. This increased risk for E, F and J would not have been identified from the DVHs. These initial results support the notion that there is additional benefit from incorporating DSMs into dose-toxicity analyses.

A limitation of this work was the lack of availability of images and contours for the most inferior part of the rectum, owing to this being located away from the planning target volume and

therefore not scanned for image guidance purposes. Some data were missing for 9/10 participants, with a median of four missing slices per scan (6-mm slice thickness). Fortunately, this part of the rectum is known to have little variation in size and shape.^{21,58} Where shown, contouring of this area was challenging: the superior aspect of the pelvic muscles provided a level below which the wall of the rectum could not be clearly seen on the MV CT scans. We have previously investigated interobserver contouring of this part of the rectum using deliberately extended image guidance scans.⁵⁹ We found that median Jaccard conformity index above the superior pelvic muscles was 0.84, interquartile range (IQR) 0.80–0.87. The corresponding value below the muscles was 0.62, IQR 0.53–0.72. Using independent-samples Kruskal–Wallis test, there was a significant difference between upper and lower portions of the rectum ($p < 0.001$). We suggest that deforming the kV planning outlines onto the MV scans is a pragmatic solution for obtaining lower rectal contours. This will be our strategy in the future where MV slices are unavailable for dose recalculation.

To test whether NTCP based on D_A is more accurate than with planned dose, large numbers of participants are required, with RT planning, D_A , and detailed late toxicity data. VoxTox has been set up with this in mind, with anticipated recruitment of 1200 participants treated for prostate cancer. We are developing automated software for contouring and will assess the added value of incorporating voxel tracking using a biomechanical modelling approach. Baseline data will capture intrinsic patient factors and all participants will be offered entry into the Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy (RAPPER) study, which is assessing polymorphisms for predicting the effects of RT.⁵⁶ We plan to develop NTCP models that incorporate D_A as a co-variate in addition to planned dose; in the future, intrinsic factors and radiogenomics may become parameters to add to the model.

We propose that this strategy to calculate D_A would enable more accurate NTCP prediction for each individual undergoing RT

for prostate cancer. The delivered dose per pixel could be calculated in real time, with updating of NTCP during the treatment course. For those cases where accumulating dose is suggestive of high NTCP, adaptive re-planning could be undertaken to reduce this to normal levels. This approach would have benefited 1/10 of our participants; if our group is indeed a good estimate of the population then re-planning 10% of patients in clinical practice would be feasible. In cases, where the rectal dose has already been planned to be as low as achievable without compromising target volume coverage, the re-planning could inform decisions on the costs and benefits of reducing the prescribed dose. Conversely, where low NTCP was anticipated, there might be potential for safe dose escalation to tumour. 4/10 of our participants had lower accumulated dose-volumes than those planned and potentially could have tolerated dose escalation to tumour without increasing their NTCP.

CONCLUSION

Accumulated dose-volumes were different from those planned in 10/10 participants, as measured by gEUD and constraints from recent trials. DSMs provided information additional to the DVH data: four participants had lower D_A s and volumes than planned, but each had pixels on the DSM that received ≥ 5 Gy more than was planned. Further work is needed to extract the dose data embedded in the DSMs. These will be correlated with toxicity as part of the VoxTox Programme.

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REFERENCES

1. Cancer statistics registrations, England (series MB1)—no 43, 2012. [Cited 14 February 2015]. Available from: <http://www.ons.gov.uk/ons/re/vs01/cancer-statistics-registrations-england-series-mb1-no-43-2012/index.html>
2. Prostate cancer incidence statistics. [Cited 14 February 2015]. Available from: <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/incidence/>
3. Cancer survival for common cancers. [Cited 14 February 2015]. Available from: <http://www.cancerresearchuk.org/cancer-info/cancerstats/survival/common-cancers/>
4. Kupelian PA, Potters L, Khuntia D, Ciezki JP, Reddy CA, Reuther AM, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; **58**: 25–33. doi: [10.1016/S0360-3016\(03\)00784-3](https://doi.org/10.1016/S0360-3016(03)00784-3)
5. Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014; **15**: 464–73. doi: [10.1016/S1470-2045\(14\)70040-3](https://doi.org/10.1016/S1470-2045(14)70040-3)
6. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol* 2014; **110**: 104–9. doi: [10.1016/j.radonc.2013.09.026](https://doi.org/10.1016/j.radonc.2013.09.026)
7. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American college of radiology 95-09. *J Clin Oncol* 2010; **28**: 1106–11. doi: [10.1200/JCO.2009.25.8475](https://doi.org/10.1200/JCO.2009.25.8475)
8. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J*

- Radiat Oncol Biol Phys* 2008; **70**: 67–74. doi: [10.1016/j.ijrobp.2007.06.054](https://doi.org/10.1016/j.ijrobp.2007.06.054)
9. Beckendorf V, Guerif S, Le Prise E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1056–63. doi: [10.1016/j.ijrobp.2010.03.049](https://doi.org/10.1016/j.ijrobp.2010.03.049)
 10. Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, Cowan RA, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; **8**: 475–87. doi: [10.1016/S1470-2045\(07\)70143-2](https://doi.org/10.1016/S1470-2045(07)70143-2)
 11. Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, Dielwart MF, et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **72**: 980–8. doi: [10.1016/j.ijrobp.2008.02.073](https://doi.org/10.1016/j.ijrobp.2008.02.073)
 12. Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1124–9. doi: [10.1016/j.ijrobp.2007.11.044](https://doi.org/10.1016/j.ijrobp.2007.11.044)
 13. Jani AB, Su A, Correa D, Gratzle J. Comparison of late gastrointestinal and genitourinary toxicity of prostate cancer patients undergoing intensity-modulated versus conventional radiotherapy using localized fields. *Prostate Cancer Prostatic Dis* 2007; **10**: 82–6. doi: [10.1038/sj.pcan.4500910](https://doi.org/10.1038/sj.pcan.4500910)
 14. Sharma NK, Li T, Chen DY, Pollack A, Horwitz EM, Buyyounouski MK. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in patients treated with androgen deprivation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2011; **80**: 437–44. doi: [10.1016/j.ijrobp.2010.02.040](https://doi.org/10.1016/j.ijrobp.2010.02.040)
 15. Dolezel M, Odrázka K, Vaculikova M, Vanasek J, Sefrova J, Paluska P, et al. Dose escalation in prostate radiotherapy up to 82 Gy using simultaneous integrated boost: direct comparison of acute and late toxicity with 3D-CRT 74 Gy and IMRT 78 Gy. *Strahlenther Onkol* 2010; **186**: 197–202. doi: [10.1007/s00066-010-2065-x](https://doi.org/10.1007/s00066-010-2065-x)
 16. Bekelman JE, Mitra N, Efsthathiou J, Liao K, Sunderland R, Yeboa DN, et al. Outcomes after intensity-modulated versus conformal radiotherapy in older men with nonmetastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: e325–34. doi: [10.1016/j.ijrobp.2011.02.006](https://doi.org/10.1016/j.ijrobp.2011.02.006)
 17. Kim S, Shen S, Moore DF, Shih W, Lin Y, Li H, et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol* 2011; **60**: 908–16. doi: [10.1016/j.eururo.2011.05.052](https://doi.org/10.1016/j.eururo.2011.05.052)
 18. Scaife J, Harrison K, Romanchikova M, Parker A, Sutcliffe M, Bond S, et al. Random variation in rectal position during radiotherapy for prostate cancer is two to three times greater than that predicted from prostate motion. *Br J Radiol* 2014; **87**: 20140343. doi: [10.1259/bjr.20140343](https://doi.org/10.1259/bjr.20140343)
 19. Chen L, Paskalev K, Xu X, Zhu J, Wang L, Price RA, et al. Rectal dose variation during the course of image-guided radiation therapy of prostate cancer. *Radiother Oncol* 2010; **95**: 198–202. doi: [10.1016/j.radonc.2010.02.023](https://doi.org/10.1016/j.radonc.2010.02.023)
 20. Engels B, Tournel K, Soete G, Storme G. Assessment of rectal distention in radiotherapy of prostate cancer using daily megavoltage CT image guidance. *Radiother Oncol* 2009; **90**: 377–81. doi: [10.1016/j.radonc.2008.12.005](https://doi.org/10.1016/j.radonc.2008.12.005)
 21. Hoogeman MS, van Herk M, de Bois J, Muller-Timmermans P, Koper PC, Lebesque JV. Quantification of local rectal wall displacements by virtual rectum unfolding. *Radiother Oncol* 2004; **70**: 21–30. doi: [10.1016/j.radonc.2003.11.015](https://doi.org/10.1016/j.radonc.2003.11.015)
 22. Lebesque JV, Bruce AM, Kroes AP, Touw A, Shouman RT, van Herk M. Variation in volumes, dose-volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 prostate cancer. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1109–19. doi: [10.1016/0360-3016\(95\)00253-7](https://doi.org/10.1016/0360-3016(95)00253-7)
 23. Murthy V, Shukla P, Adurkar P, Master Z, Mahantshetty U, Shrivastava SK. Dose variation during hypofractionated image-guided radiotherapy for prostate cancer: planned versus delivered. *J Cancer Res Ther* 2011; **7**: 162–7. doi: [10.4103/0973-1482.82920](https://doi.org/10.4103/0973-1482.82920)
 24. Peng C, Ahunbay E, Chen G, Anderson S, Lawton C, Li XA. Characterizing interfraction variations and their dosimetric effects in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; **79**: 909–14. doi: [10.1016/j.ijrobp.2010.05.008](https://doi.org/10.1016/j.ijrobp.2010.05.008)
 25. Roeske JC, Forman JD, Mesina CF, He T, Pelizzari CA, Fontenla E, et al. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1321–9. doi: [10.1016/0360-3016\(95\)00225-1](https://doi.org/10.1016/0360-3016(95)00225-1)
 26. van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1311–20. doi: [10.1016/0360-3016\(95\)00116-6](https://doi.org/10.1016/0360-3016(95)00116-6)
 27. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012; **13**: 43–54. doi: [10.1016/S1470-2045\(11\)70293-5](https://doi.org/10.1016/S1470-2045(11)70293-5)
 28. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76**(Suppl. 3): S10–19. doi: [10.1016/j.ijrobp.2009.07.1754](https://doi.org/10.1016/j.ijrobp.2009.07.1754)
 29. Hatton JA, Greer PB, Tang C, Wright P, Capp A, Gupta S, et al. Does the planning dose-volume histogram represent treatment doses in image-guided prostate radiation therapy? Assessment with cone-beam computerised tomography scans. *Radiother Oncol* 2011; **98**: 162–8. doi: [10.1016/j.radonc.2011.01.006](https://doi.org/10.1016/j.radonc.2011.01.006)
 30. Kupelian PA, Langen KM, Zeidan OA, Meeks SL, Willoughby TR, Wagner TH, et al. Daily variations in delivered doses in patients treated with radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2006; **66**: 876–82. doi: [10.1016/j.ijrobp.2006.06.011](https://doi.org/10.1016/j.ijrobp.2006.06.011)
 31. Akino Y, Yoshioka Y, Fukuda S, Maruoka S, Takahashi Y, Yagi M, et al. Estimation of rectal dose using daily megavoltage cone-beam computed tomography and deformable image registration. *Int J Radiat Oncol Biol Phys* 2013; **87**: 602–8. doi: [10.1016/j.ijrobp.2013.06.2054](https://doi.org/10.1016/j.ijrobp.2013.06.2054)
 32. The VoxTox research programme. [Cited 8 June 2015]. Available from: <http://www.voxtox.org>
 33. Burnet NG, Adams EJ, Fairfoul J, Tudor GS, Hoole AC, Routsis DS, et al. Practical aspects of implementation of helical tomotherapy for intensity-modulated and image-guided radiotherapy. *Clin Oncol* 2010; **22**: 294–312. doi: [10.1016/j.clon.2010.02.003](https://doi.org/10.1016/j.clon.2010.02.003)
 34. Romanchikova M, Burnet N, Harrison K, Hoole A, Parker A, Thomas S, eds. *The challenge of generating DICOM RT data from TomoTherapy archives for the VoxTox study*. 2013 IPem Conference—Data: Storage, Management, Generation and Legislation; 16 April 2013; London, UK. [Updated 8 June 2015]. Available from: <http://www.ipem.ac.uk/Portals/0/Documents/Conferences/2013%20programmes/Conference%20Abstracts%202013.pdf>
 35. Thomas SJ, Eyre KR, Tudor GS, Fairfoul J. Dose calculation software for helical tomotherapy, utilizing patient CT data to calculate

- an independent three-dimensional dose cube. *Med Phys* 2012; **39**: 160–7. doi: [10.1118/1.3668061](https://doi.org/10.1118/1.3668061)
36. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010; **76**(Suppl. 3): S123–9. doi: [10.1016/j.ijrobp.2009.03.078](https://doi.org/10.1016/j.ijrobp.2009.03.078)
 37. Fiorino C, Fellin G, Rancati T, Vavassori V, Bianchi C, Borca VC, et al. Clinical and dosimetric predictors of late rectal syndrome after 3D-CRT for localized prostate cancer: preliminary results of a multicenter prospective study. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1130–7. doi: [10.1016/j.ijrobp.2007.07.2354](https://doi.org/10.1016/j.ijrobp.2007.07.2354)
 38. Khoo VS, Dearnaley DP. Question of dose, fractionation and technique: ingredients for testing hypofractionation in prostate cancer—the CHHiP trial. *Clin Oncol* 2008; **20**: 12–14. doi: [10.1016/j.clon.2007.10.008](https://doi.org/10.1016/j.clon.2007.10.008)
 39. Murray J, McQuaid D, Dunlop A, Buettner F, Nill S, Hall E, et al. A novel approach to evaluate the dosimetric effect of rectal variation during image guided prostate radiotherapy. *Med Phys* 2014; **41**: 157. doi: [10.1118/1.4888065](https://doi.org/10.1118/1.4888065)
 40. Buettner F, Gulliford SL, Webb S, Partridge M. Using Bayesian logistic regression to evaluate a new type of dosimetric constraint for prostate radiotherapy treatment planning. *Med Phys* 2010; **37**: 1768–77. doi: [10.1118/1.3367013](https://doi.org/10.1118/1.3367013)
 41. Dearnaley DP, Hall E, Lawrence D, Huddart RA, Eeles R, Nutting CM, et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005; **92**: 488–98. doi: [10.1038/sj.bjc.6602301](https://doi.org/10.1038/sj.bjc.6602301)
 42. Tucker SL, Dong L, Bosch WR, Michalski J, Winter K, Mohan R, et al. Late rectal toxicity on RTOG 94-06: analysis using a mixture Lyman model. *Int J Radiat Oncol Biol Phys* 2010; **78**: 1253–60. doi: [10.1016/j.ijrobp.2010.01.069](https://doi.org/10.1016/j.ijrobp.2010.01.069)
 43. Sohn M, Yan D, Liang J, Meldolesi E, Vargas C, Alber M. Incidence of late rectal bleeding in high-dose conformal radiotherapy of prostate cancer using equivalent uniform dose-based and dose-volume-based normal tissue complication probability models. *Int J Radiat Oncol Biol Phys* 2007; **67**: 1066–73.
 44. Rancati T, Fiorino C, Gagliardi G, Cattaneo GM, Sanguineti G, Borca VC, et al. Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101). *Radiother Oncol* 2004; **73**: 21–32. doi: [10.1016/j.radonc.2004.08.013](https://doi.org/10.1016/j.radonc.2004.08.013)
 45. Peeters ST, Hoogeman MS, Heemsbergen WD, Hart AA, Koper PC, Lebesque JV. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: normal tissue complication probability modeling. *Int J Radiat Oncol Biol Phys* 2006; **66**: 11–19. doi: [10.1016/j.ijrobp.2006.03.034](https://doi.org/10.1016/j.ijrobp.2006.03.034)
 46. Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys* 1991; **21**: 123–35. doi: [10.1016/0360-3016\(91\)90172-Z](https://doi.org/10.1016/0360-3016(91)90172-Z)
 47. Peeters ST, Lebesque JV, Heemsbergen WD, van Putten WL, Slot A, Dielwart MF, et al. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1151–61. doi: [10.1016/j.ijrobp.2005.10.002](https://doi.org/10.1016/j.ijrobp.2005.10.002)
 48. Greco C, Mazzetta C, Cattani F, Tosi G, Castiglioni S, Fodor A, et al. Finding dose-volume constraints to reduce late rectal toxicity following 3D-conformal radiotherapy (3D-CRT) of prostate cancer. *Radiother Oncol* 2003; **69**: 215–22. doi: [10.1016/j.radonc.2003.08.003](https://doi.org/10.1016/j.radonc.2003.08.003)
 49. Akimoto T, Muramatsu H, Takahashi M, Saito J, Kitamoto Y, Harashima K, et al. Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. *Int J Radiat Oncol Biol Phys* 2004; **60**: 1033–9. doi: [10.1016/j.ijrobp.2004.07.695](https://doi.org/10.1016/j.ijrobp.2004.07.695)
 50. Vargas C, Martinez A, Kestin LL, Yan D, Grills I, Brabbs DS, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; **62**: 1297–308. doi: [10.1016/j.ijrobp.2004.12.052](https://doi.org/10.1016/j.ijrobp.2004.12.052)
 51. Gulliford SL, Foo K, Morgan RC, Aird EG, Bidmead AM, Critchley H, et al. Dose-volume constraints to reduce rectal side effects from prostate radiotherapy: evidence from MRC RT01 Trial ISRCTN 47772397. *Int J Radiat Oncol Biol Phys* 2010; **76**: 747–54. doi: [10.1016/j.ijrobp.2009.02.025](https://doi.org/10.1016/j.ijrobp.2009.02.025)
 52. Jackson A, Skwarchuk MW, Zelefsky MJ, Cowen DM, Venkatraman ES, Levegrun S, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys* 2001; **49**: 685–98. doi: [10.1016/S0360-3016\(00\)01414-0](https://doi.org/10.1016/S0360-3016(00)01414-0)
 53. Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. Assessing correlations between the spatial distribution of the dose to the rectal wall and late rectal toxicity after prostate radiotherapy: an analysis of data from the MRC RT01 trial (ISRCTN 47772397). *Phys Med Biol* 2009; **54**: 6535–48. doi: [10.1088/0031-9155/54/21/006](https://doi.org/10.1088/0031-9155/54/21/006)
 54. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer* 2009; **9**: 134–42. doi: [10.1038/nrc2587](https://doi.org/10.1038/nrc2587)
 55. Barnett GC, Thompson D, Fachal L, Kerns S, Talbot C, Elliott RM, et al. A genome wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity. *Radiother Oncol* 2014; **111**: 178–85. doi: [10.1016/j.radonc.2014.02.012](https://doi.org/10.1016/j.radonc.2014.02.012)
 56. Burnett NG, Barnett GC, Elliott RM, Dearnaley DP, Pharoah PD, Dunning AM, et al. RAPPER: the radiogenomics of radiation toxicity. *Clin Oncol* 2013; **25**: 431–4. doi: [10.1016/j.clon.2013.04.001](https://doi.org/10.1016/j.clon.2013.04.001)
 57. Munbodh R, Jackson A, Bauer J, Schmidlein C, Zelefsky M. Spatial and anatomical indicators of rectal toxicity in IMRT of prostate cancer. *Int J Radiat Oncol Biol Phys* 2007; **69**(Suppl. 1): S10–11. doi: [10.1016/j.ijrobp.2007.07.020](https://doi.org/10.1016/j.ijrobp.2007.07.020)
 58. Chong I, Hawkins M, Hansen V, Thomas K, McNair H, O'Neill B, et al. Quantification of organ motion during chemoradiotherapy of rectal cancer using cone-beam computed tomography. *Int J Radiat Oncol Biol Phys* 2011; **81**: e431–8. doi: [10.1016/j.ijrobp.2011.04.060](https://doi.org/10.1016/j.ijrobp.2011.04.060)
 59. Scaife J, Harrison K, Drew A, Cai X, Lee J, Schonlieb C-B, et al. Accuracy of manual and automated rectal contours using helical tomotherapy image guidance scans during prostate radiotherapy. *J Clin Oncol* 2015; **33**(Suppl. 7): 94.