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FULL PAPER

Parametrized rectal dose and associations with late toxicity in prostate cancer radiotherapy

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Objective: We investigated possible associations between planned dose-volume parameters and rectal late toxicity in 170 patients having radical prostate cancer radiotherapy.

Methods: For each patient, the rectum was outlined from anorectal junction to sigmoid colon, and rectal dose was parametrized using dose-volume (DVH), dose-surface (DSH) and dose-line (DLH) histograms. Generation of DLHs differed from previous studies in that the rectal dose was parametrized without first unwrapping onto 2-dimensional dose-surface maps. Patient-reported outcomes were collected using a validated Later Effects in Normal Tissues Subjective, Objective, Management and Analytic questionnaire. Associations between dose and toxicity were assessed using a one-sided Mann-Whitney *U* test.

Results: Associations ($p < 0.05$) were found between equieffective dose (EQD2₃) and late toxicity as follows:

overall toxicity with DVH and DSH at 13–24 Gy; proctitis with DVH and DSH at 25–36 Gy and with DVH, DSH and DLH at 61–67 Gy; bowel urgency with DVH and DSH at 10–20 Gy. None of these associations met statistical significance following the application of a Bonferroni correction.

Conclusion: Independently confirmed associations between rectal dose and late toxicity remain elusive. Future work to increase the accuracy of the knowledge of the rectal dose, either by accounting for interfraction and intrafraction rectal motion or via stabilization of the rectum during treatment, may be necessary to allow for improved dose-toxicity comparisons.

Advances in knowledge: This study is the first to use parametrized DLHs to study associations with patient-reported toxicity for prostate radiotherapy showing that it is feasible to model rectal dose mapping in three dimensions.

INTRODUCTION

Dose escalation of radiotherapy improves local and biochemical control of localized prostate cancer.^{1–3} However, rectal toxicity is a dose-limiting factor,^{4–7} and identification of an isotoxic dose to the rectum would facilitate dose escalation with potential benefits in disease outcome.

Investigations into possible associations between rectal toxicity and dose received during radiotherapy treatment for prostate cancer have been plentiful. Most work has looked at dose-volume histogram (DVH) parameters and whether any significant links with toxicity can be identified.^{8–11}

Further studies^{12,13} have looked at not only the rectum but also additional structures, e.g. pelvic floor muscles. However, the DVH alone provides no anatomical dose information and other parametrizations of the dose data may be more suitable for identification of associations between dose and toxicity. Work into extracting more dose information from the treatment planning system (TPS) has been undertaken by various groups.^{14–19}

Many previous studies investigating methods of parametrizing the rectal dose are based on techniques which unwrap the three-dimensional (3D) surface of

the organ to provide a two-dimensional (2D) dose–surface map (DSM).^{15,19,20} Buettner *et al*¹⁵ included an assessment of the longitudinal and lateral extent of the dose to the rectum, fitting an ellipse to the 2D DSM with the size (in terms of the projection of the major and minor axes of the ellipse on to the x and y axes of the DSM) and eccentricity being used as parametrization metrics. Evaluation of 2D DSMs has also been employed to compare rectal doses to endoscopic inspections to investigate the use of an endorectal balloon (ERB) during treatment.²¹ Tucker *et al*¹⁹ used cluster models to assess spatial aspects of unwrapped dose matrices.

Other studies have used principal component analysis (PCA) to investigate associations between rectal dose and late toxicity.^{22,23} However, PCA cannot be readily applied when the cohort consists of several different radiotherapy techniques owing to the variability in the dose distributions.²³ We have therefore not applied PCA in the present study.

The study investigated possible associations between rectal dose and late toxicity using four different parametrization metrics, aiming to assess whether associations reported by Buettner *et al*¹⁵ could be validated using our independent patient cohort. Software developed in-house enabled rectal dose to be

Figure 1. (a) A typical rectal geometry showing equieffective dose with 2 Gy absorbed dose per fraction and $\alpha/\beta = 3$ Gy (EQD2₃) at the surface voxels. Axes units are centimetres. The length for dose–line histograms in the lateral (DL_{lat}H) is extracted by taking dose–line histograms around the circumference of each slice of the rectum. (b) Plot showing the dose–line histograms around each slice of the rectum (grey lines) from which the DL_{lat}H is obtained by taking the upper limit (black line). (c) The length for dose–line histograms in the longitudinal (DL_{long}H) is extracted by taking the maximum length of the isodose region for each dose level, this example, showing the lengths of the 54 and 60 Gy isodose regions. (d) The extracted dose–volume histogram (DVH), dose–surface histogram (DSH), DL_{lat}H and DL_{long}H.

parametrized without the use of 2D DSMs, thereby avoiding potential inaccuracies which can be introduced during the unwrapping of the rectal geometry.

METHODS AND MATERIALS

Dose evaluation methodology

Two methods of outlining the rectum were assessed prior to the study to compare the impact of using different superior and inferior limits. In the standard outlining method, the rectum was outlined from the anorectal junction to the sigmoid colon, whereas in the alternative method, the rectal outline was limited 5 mm superior and inferior of the planning target volume. The impact on the resulting DVHs was assessed and while the truncated outlining method affected the DVHs at low dose levels (since truncation removes regions receiving the lowest doses or no dose at all), at higher dose levels the impact was small. To ensure that the results of the present dose–toxicity study are generally transferable, we used the standard outlining method for the assessment of rectal dose.

The dose to each rectum was parametrized using DVH, dose–surface (DSH) and dose–line histograms in the lateral (DL_{lat}H) and longitudinal (DL_{long}H) directions as follows:

- DVH: formation replicates that of any commercial TPS.
- DSH: only the surface voxels of the 3D geometry are included, with the superior and inferior slices also being counted as open since the rectum forms a hollow tube.
- DL_{lat}H: formed by taking the upper limit (worst case) of histograms for all slices of the rectum. [Figure 1a,b](#) illustrates this for an example patient: [Figure 1a](#) shows the geometry of the rectum, consisting of 39 slices stacked in the z-direction. A dose–line histogram (DLH) is computed for the voxels on the outer circumference of each slice, giving 39 DLHs (shown in grey in [Figure 1b](#)). The DL_{lat}H is formed by taking the upper limit of these (as shown by the black line in [Figure 1b](#)) and is thus a measure of the fraction of the circumference covered by the isodose region at its widest point.
- DL_{long}H: formed by recording the length of the isodose region in the superior–inferior direction for each dose level ([Figure 1c](#)).

[Figure 1d](#) illustrates all four histograms (DVH, DSH, DL_{lat}H and DL_{long}H) for the sample rectum.

The method of forming both the DL_{lat}H and DL_{long}H assumes that the isodose region consists of a single continuous area. In cases where the isodose region is split into multiple parts, the total length bounded by these parts was recorded.

The in-house dose parametrization software was written using MATLAB® (MathWorks®, Natick, MA) and was capable of running in batch mode to parametrize the full patient cohort in semi-automated fashion. The code worked directly from the 3D dose data, eliminating the use of 2D DSMs. This avoids the following potential difficulties:

- (1) The rectum typically has a complex geometry which cannot be adequately modelled by considering it as a simple tube. The process of unwrapping the 3D rectum to form a 2D DSM inevitably warps the shape of the dose map. The rectal geometry in [Figure 1](#) demonstrates this, having a complex

shape which is difficult to unwrap without introducing some degree of distortion to the resulting 2D dose–surface map.

- (2) Once unwrapped, the isodose regions in the 2D dose map are not inherently geometrical, and so methods which fit these regions using geometric shapes¹⁵ potentially introduce a source of uncertainty. In addition, any warp that was introduced during the unwrapping stage will impact on the geometry of isodose regions in 2D.
- (3) The particular case of using ellipses for the fit to the 2D dose map¹⁵ leads to a further potential source of uncertainty for cases where the ellipse is close to circular, since the orientation of a circle is arbitrary owing to rotational symmetry. If the projection of the ellipse axes onto the DSM axes is used as a dose metric, then the values for the projected size could differ by a factor of up to $1/\sqrt{2}$ depending on the orientation of the circle. In addition, since the isodose regions in the DSM are not inherently elliptical, it is likely that such close-to-circular fits may occur frequently.

The treatment plans were all outlined and planned using the Pinnacle³ TPS v. 7.4 and 8.0 (Philips Medical Systems, Eindhoven, Netherlands).

Patient cohort

The patient cohort consisted of 170 patients treated at a single comprehensive cancer centre between 2005 and 2009. The cohort comprised several treatment techniques and fractionation schemes according to evolving practice, as shown in [Table 1](#). Standard practice was that patients did not receive bowel preparation, and no rectal stabilization devices (such as ERBs) were used.

Mean age at treatment was 65.1 years (48.1–75.5 years). Follow-up was performed in 2011, with at least a 2-year interval following treatment. Prospective assessment of bowel toxicity was performed using a validated Later Effects in Normal Tissues Subjective, Objective, Management and Analytic (LENT-SOMA) scale, by means of a questionnaire completed by the patient between April and May 2011 and returned by post. Toxicity in each category was marked on a scale of zero to four, with higher scores corresponding to more severe toxicity. The collated results showed that 58% of those who responded experienced at least one toxicity of $\geq$ grade 2. The number of patients reporting each category of toxicity is shown in [Table 2](#).

Equieffective dose

All dose values were converted to equieffective dose with 2 Gy absorbed dose per fraction (EQD2)²⁴ using the linear-quadratic model to standardize the cohort. An alpha/beta ratio of 3 Gy was used for the rectum.²⁵

The majority of published data was based upon standard 2 Gy-per-fraction treatment schedules.^{8,9,26} Dose escalation and hypofractionation regimes have recently become more prevalent, and so the conclusions of these previously published studies may not necessarily be extrapolated to the group within the present study.

Statistical analysis of dose and toxicity data

A statistical analysis was performed to test for possible links between toxicity and each of the four dose parametrizations.

Table 1. Summary of the treatment regimes for all patients (170 in total) in the cohort

Fractionation	Technique	Number of patients
50.0 Gy for 16 fractions	3D-CRT	63
52.5 Gy for 20 fractions	3D-CRT	11
50.0 Gy for 20 fractions	3D-CRT	1
57.0 Gy for 19 fractions	IMRT	79
74.0 Gy for 37 fractions	IMRT	9
60.0 Gy for 20 fractions	IMRT	7

3D, three-dimensional; CRT, conformal radiation therapy; IMRT, intensity-modulated radiotherapy.

This section outlines the procedure used to assess the DVH, but the same process can be considered for the other parametrizations (substituting “area” or “length” for “volume” as appropriate).

For each toxicity category, the patients were first split into two groups: one group containing all patients having LENT-SOMA toxicity scores of zero or one (considered here as an absence of toxicity) and the other group containing all patients having scores of two, three or four (considered as a presence of toxicity).

For each patient, the DVH was assessed at each dose level (from 1 to 72 Gy EQD_{2.3} in 1-Gy steps), and the volume of rectum receiving that dose was extracted to provide two sets of volume data: one for the no-toxicity group and the other for the toxicity group. These two data sets were assessed using a one-sided Mann–Whitney *U* test to examine whether the volumes for each group were statistically different, with null hypothesis being that there was no difference.

When selecting an appropriate significance level, the multiplicity of the analysis must be considered, since the likelihood of false positives (associations arising purely by chance) grows with the number of tests performed. To account for this, the threshold for significance can be lowered using a Bonferroni correction.²⁷ However, this comes with a corresponding increase in the risk of false negatives (missing actual associations).²⁸ We therefore present results both with and without a Bonferroni correction to account for multiplicity. Significance levels of $p \leq 0.05$ and $p \leq 0.05 N^{-1}$ were applied for the uncorrected and corrected analyses, respectively, where *N* was the total number of independent hypotheses under test. Since four parametrizations were under test, *N* can be represented by $4n$, where *n* is the number of hypotheses under test for each parametrization. While 72 separate statistical tests were performed for each parametrization (from 1 to 72 Gy EQD_{2.3} in 1-Gy steps), these cannot be considered independent. We consider 6 Gy to be an appropriate interval for independence

and have therefore applied a corresponding Bonferroni correction factor of $N = 4 \times 72/6 = 48$, with a *p*-value threshold for statistical significance of $0.05 N^{-1} = 0.0010$.

The analysis did not seek to test whether the technique (conformal radiation therapy or intensity-modulated radiotherapy) or fractionation affected toxicity.

RESULTS

Results of the analysis of dose and toxicity data are summarized in Figure 2 and in Table 3.

Considering the results without the Bonferroni correction, strong associations were found between parametrized equi-effective dose (EQD_{2.3}) and late toxicity for the following conditions: overall toxicity with DVH and DSH at 13–24 Gy; proctitis with DVH and DSH at 25–36 Gy and with DVH, DSH, DL_{lat}H and DL_{long}H at 61–67 Gy; Bowel urgency with DVH and DSH at 10–20 Gy. More tenuous associations were also observed for: urgency with DL_{lat}H at 33 Gy; faecal incontinence with DVH and DSH at 18 Gy; rectal bleeding with DVH and DSH at 21 Gy. A complete list of the identified associations is given in Table 3.

When applying the Bonferroni correction with $N = 48$, none of the aforementioned associations met the threshold for statistical significance.

DISCUSSION

Our study is similar to Buettner *et al*¹⁵ in terms of the general approach (parametrization of the dose to the rectum) and minimum follow-up (2 years), and one of our aims was to investigate whether we could independently validate their reported associations, which were as follows:

- Proctitis: lateral extent at 62 Gy (59 Gy EQD_{2.3}).
- Loose stools: DSH at 22–30 Gy (17–23 Gy EQD_{2.3}); longitudinal extent at 22–34 Gy (16–27 Gy EQD_{2.3}); eccentricity 22–26 Gy (16–20 Gy EQD_{2.3}).
- Rectal bleeding: DSH at 52 Gy (47 Gy EQD_{2.3}); lateral extent at 40–44 Gy (33–37 Gy EQD_{2.3}) and 52–60 Gy (47–57 Gy EQD_{2.3}).

Table 2. Number of patients having toxicity at Later Effects in Normal Tissues Subjective, Objective, Management and Analytic Level 2 or higher for each toxicity category

Category	Number of patients with toxicity at Level 2 or higher
Proctitis	24 (14.1%)
Urgency	82 (48.2%)
Loose stools	4 (2.4%)
Incontinence	8 (4.7%)
Rectal bleeding	11 (6.5%)
Constipation	27 (15.9%)
Combined toxicity	106 (62.4%)

Figure 2. The results of the statistical analysis, showing the p -value for associations between (a) proctitis, (b) urgency, (c) faecal incontinence, (d) rectal bleeding, (e) constipation and (f) overall toxicity with parametrized dose [dose-volume histogram (DVH), dose-surface histogram (DSH), dose-line histograms in the lateral (DL_{latH}) and dose-line histograms in the longitudinal (DL_{longH})]. Results were calculated using a one-sided Mann-Whitney U test. The dashed and dotted lines indicate p -value thresholds of 0.05 (without Bonferroni correction) and $0.05N^{-1}$ (with Bonferroni correction, using $N = 44$), respectively.

Table 3. Toxicity types, parametrizations and dose levels where statistically significant associations were found between toxicity and dose parametrization. The “parametrization score” represents volume for dose–volume histograms (DVHs), surface area for dose–surface histograms (DSHs) and length for dose–line histograms in the lateral (DL_{lat}H) and the longitudinal (DL_{long}H) directions

Toxicity type	Parametrization	Equieffective dose with 2 Gy absorbed dose per fraction and $\alpha/\beta = 3$ Gy (Gy)	Parametrization score (%) for patients without toxicity (mean $\pm$ SD)	Parametrization score (%) for patients with toxicity (mean $\pm$ SD)	Number of patients (with toxicity/all)	<i>p</i> -value
Proctitis	DVH	28	68.6 $\pm$ 15.5	77.6 $\pm$ 10.4	24/170	0.0027
Proctitis	DSH	28	67.6 $\pm$ 13.4	75.5 $\pm$ 9.8	24/170	0.0016
Proctitis	DVH	64	3.5 $\pm$ 4.4	5.0 $\pm$ 3.7	24/170	0.0132
Proctitis	DSH	64	6.4 $\pm$ 6.9	9.3 $\pm$ 6.2	24/170	0.0166
Proctitis	DL _{lat} H	64	21.5 $\pm$ 21.7	32.9 $\pm$ 23.7	24/170	0.0290
Proctitis	DL _{long} H	64	28.6 $\pm$ 29.0	40.9 $\pm$ 26.0	24/170	0.0277
Urgency	DVH	13	55.6 $\pm$ 45.7	69.5 $\pm$ 41.5	84/170	0.0101
Urgency	DSH	13	55.3 $\pm$ 45.4	69.3 $\pm$ 41.3	84/70	0.0104
Faecal incontinence	DVH	18	69.0 $\pm$ 38.3	92.6 $\pm$ 7.4	8/170	0.0241
Faecal incontinence	DSH	18	68.8 $\pm$ 38.1	91.6 $\pm$ 8.0	8/170	0.0324
Rectal bleeding	DVH	18	69.2 $\pm$ 38.2	84.2 $\pm$ 28.5	11/170	0.0419
Rectal bleeding	DSH	18	68.9 $\pm$ 38.0	84.0 $\pm$ 28.2	11/170	0.0408
Combined toxicity	DVH	18	62.7 $\pm$ 40.8	74.6 $\pm$ 35.3	106/170	0.0052
Combined toxicity	DSH	18	62.3 $\pm$ 40.5	74.5 $\pm$ 35.1	106/170	0.0038

SD, standard deviation.

In comparison, for proctitis, we found a strong association with both DVH and DSH at 25–36 Gy EQD₂ and weaker associations between proctitis and DVH, DSH, lateral extent and longitudinal extent at 61–67 Gy EQD₂. The reason for this difference from Buettner *et al*,¹⁵ who found only an association with lateral extent, is unclear. For loose stools, the number of patients reporting rectal toxicity in our cohort was too small to permit a valid statistical analysis. For rectal bleeding, we found an association with DSH at a much lower dose level than Buettner *et al*,¹⁵ but not for lateral extent (albeit an association with lateral extent at EQD₂ = 41 Gy was close to significance in our study, with $p = 0.080$).

Our study differs from Buettner *et al*¹⁵ in terms of the patient cohort, toxicity grading scheme, radiotherapy technique, fractionation scheme and the details of the dose parametrisation and statistical analysis methods, all of which are possible reasons for the different results found. The difference between the findings highlights the difficulty in making generalizations regarding the dose tolerance level of the rectum. The findings may be limited

by other confounding factors, preventing their extrapolation to other studies. In particular, associations could potentially arise as a consequence of the tendency of prescriptive treatment planning methods to generate plans with similar dose distributions. As a result, there is a need for publication of further results for cross-validation from different centres, ideally in the form of multicentre studies.

It should be noted that even if the observed associations between dose and toxicity were assumed to be an accurate guide to the radiation tolerance of the rectum, they would not currently be sufficient to provide a means of predicting rectal toxicity in advance for individual patients. This is because the spread in the parametrized dose scores (*i.e.* volume for DVH, surface area for DSH and length for DL_{lat}H and DL_{long}H) in patients with or without toxicity is wide relative to the difference in the mean scores. That is, the distributions of scores for the no-toxicity and toxicity groups substantially overlap. This is illustrated in Table 3, where for all toxicity types, the difference in parametrization scores between the no-toxicity and toxicity groups is

always <1 standard deviation of either of the two groups. (The exception is for faecal incontinence, where the difference in the means is approximately three standard deviations of the toxicity group for both DVH and DSH. The DVH and DSH scores at 18 Gy could therefore potentially be used to predict an absence, but not a presence, of faecal incontinence.) Additionally, it should be emphasized that association does not demonstrate causation.

Results showed that the DVH and DSH parametrizations provided fundamentally similar results, as shown in Figure 2 where the DVH and DSH data follow each other closely for all toxicity types. This is not unexpected, since the DVH and DSH themselves typically have a very similar shape, as in the example in Figure 1d. This suggests that the DVH is an acceptable parameter for assessment of dose to the rectum, even though it is only the rectal wall which is anatomically relevant. Several current TPSs have the ability to provide DVH but not DSH data, and our results suggest that this may not be an important limitation when assessing rectal doses.

The presented results show that $DL_{lat}H$ and $DL_{long}H$ did not provide any improvement over DVH or DSH as a predictor of rectal toxicity. This could signify either that such parametrizations are of limited value or that they are more sensitive to confounding factors (such as interfraction and intrafraction motion) than DVH or DSH.

The dose parametrizations assessed in this study (DVH, DSH, $DL_{lat}H$ and $DL_{long}H$) provide a means to assess the dose received by the rectum but provide no information on the location of that dose on the rectal geometry. This is an area that may warrant further investigation.

The ability to identify associations between dose and toxicity may be limited by interfraction and intrafraction motion of the rectum. The

CT image that is used for treatment planning is a snapshot in time and may not be a representative of the actual anatomy on every day throughout the treatment. Compounding this, the rectum is an organ which is particularly prone to interfraction and intrafraction motion. There is therefore a question regarding how realistic the planned dose to the rectum is. Studies have shown that the use of an ERB during treatment is an effective method of stabilizing the rectum^{29,30} and allows the dose to the rectum to be reduced (by pushing part of the rectum away from the high-dose region) with a corresponding decrease in observed late mucosal changes of the rectal wall.²¹ Further work using the dose parametrization methods reported in the present study in conjunction with a means of stabilizing the rectum during treatment would be of interest.

Other limitations of the present study include the lack of baseline data to evaluate pre-existing rectal symptoms unrelated to radiotherapy. Also, for several toxicity categories (loose stools, incontinence, rectal bleeding), the number of events was small and a larger study is needed to fully explore any associations.

CONCLUSION

Using a validated LENT-SOMA questionnaire to quantify patient-reported late toxicity, rectal dose levels of 13–24 Gy EQD₂₃ were found to be associated with overall symptoms. Analyses of specific rectal symptoms suggest that proctitis and urgency are associated with dose levels of 25–36 Gy EQD₂₃ and 10–20 Gy EQD₂₃, respectively ($p \leq 0.05$). However, these associations are not statistically significant if a Bonferroni correction for multiple statistical analyses is applied. We are therefore unable to independently validate associations between rectal dose and late toxicity found in previous studies.^{15,16} Future work to increase the accuracy of the knowledge of the rectal dose, either by accounting for interfraction and intrafraction rectal motion or via stabilization of the rectum during treatment, may be necessary to allow associations between rectal dose and late toxicity to be reliably identified.

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