Physics and Imaging in Radiation Oncology 33 (2025) 100701

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

New rectum dose surface mapping methodology to identify rectal subregions associated with toxicities following prostate cancer radiotherapy

Artemis Bouzaki [a,*], Dylan Green [b], Marcel van Herk [a,c], Jane Shortall [a,c], Tanuj Puri [a], Sarah Kerns [d], David Azria [e], Marrie-Pierre Farcy-Jacquet [f], Jenny Chang-Claude [g,h], Ananya Choudhury [a,c], Alison Dunning [i], Maarten Lambrecht [j], Barbara Avuzzi [k], Dirk De Ruysscher [l], Petra Seibold [g], Elena Sperk [m], Christopher Talbot [n], Ana Vega [o,p,q], Liv Veldeman [r,s], Adam Webb [n], Barry Rosenstein [t], Catharine M. West [u], Eliana Gioscio [v], Tiziana Rancati [v], Eliana Vasquez Osorio [a,c,1], Alan McWilliam [a,c,1]

[a] Division of Cancer Sciences, University of Manchester, Manchester, the United Kingdom of Great Britain and Northern Ireland
[b] Department of Engineering Science, University of Oxford, Oxford, the United Kingdom of Great Britain and Northern Ireland
[c] The Christie NHS Foundation Trust, Manchester, the United Kingdom of Great Britain and Northern Ireland
[d] Medical College of Wisconsin, Milwaukee, WI, USA
[e] Federation Universitaire d'Oncologie Radiothérapie d'Occitanie Méditerranée, Univ Montpellier, INSERM U1194 IRCM, Institut du Cancer Montpellier (ICM), Montpellier, France
[f] Federation Universitaire d'Oncologie Radiothérapie d'Occitanie Méditerranée, Institut du Cancer Du Gard (ICG), CHU Carémeau, Nîmes, France
[g] German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Heidelberg, Germany
[h] University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Germany
[i] Centre for Cancer Genetic Epidemiology, Strangeways Research Laboratory, University of Cambridge, Cambridge, the United Kingdom of Great Britain and Northern Ireland
[j] KU Leuven, Leuven, Belgium
[k] Department of Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[l] Department of Radiation Oncology (Maastro), Maastricht University Medical Center+, GROW School, Maastricht, the Netherlands
[m] Department of Radiation Oncology, Universitätsmedizin Mannheim, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[n] Department of Genetics & Cancer Sciences, University of Leicester, the United Kingdom of Great Britain and Northern Ireland
[o] Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[p] Fundación Pública Galega de Medicina Xenómica (FPGMX), Santiago de Compostela, Spain
[q] Biomedical Network on Rare Diseases (CIBERER), Spain
[r] Ghent University Hospital, Belgium
[s] Ghent University, Ghent, Belgium
[t] Departments of Radiation Oncology & Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, NY, USA
[u] Translational Radiobiology Group, Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, the United Kingdom of Great Britain and Northern Ireland
[v] Data Science Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

ARTICLE INFO

Keywords:
Radiotherapy
Prostate cancer
Normal tissue toxicity
Dose surface map
Rectum mapping

ABSTRACT

Background and purpose: Growing evidence suggests that spatial dose variations across the rectal surface influence toxicity risk after radiotherapy. Existing methodologies employ a fixed, arbitrary physical extent for rectal dose mapping, limiting their analysis. We developed a method to standardise rectum contours, unfold them into 2D cylindrical surface maps, and identify subregions where higher doses increase rectal toxicities.
Materials and methods: Data of 1,048 patients with prostate cancer from the REQUITE study were used. Deep learning based automatic segmentations were generated to ensure consistency. Rectum length was standardised

* Corresponding author at: The University of Manchester, The Paterson, first floor, Wilmslow Road, Manchester, M16 7QS, the United Kingdom of Great Britain and Northern Ireland.
E-mail address: artemis.bouzaki@postgrad.manchester.ac.uk (A. Bouzaki).
[1] joint last authors.

https://doi.org/10.1016/j.phro.2025.100701
Received 21 November 2024; Received in revised form 9 January 2025; Accepted 14 January 2025
Available online 20 January 2025

using linear transformations superior and inferior to the prostate. The automatic contours were validated against the manual contours through contour variation assessment with cylindrical mapping. Voxel-based analysis of the dose surface maps for the manual and automatic contours against individual rectal toxicities was performed using Student's t permutation test and Cox Proportional Hazards Model (CPHM). Significance was defined by permutation testing.

Results: Our method enabled the analysis of 1,048 patients using automatic segmentation. Student's *t*-test showed significance ($p < 0.05$) in the lower posterior for clinical-reported proctitis and patient-reported bowel urgency. Univariable CPHM identified a 3 % increased risk per Gy for clinician-reported proctitis and a 2 % increased risk per Gy for patient-reported bowel urgency in the lower posterior. No other endpoints were significant.

Conclusion: We developed a methodology that unfolds the rectum to a 2D surface map. The lower posterior was significant for clinician-reported proctitis and patient-reported bowel urgency, suggesting that reducing the dose in the region could decrease toxicity risk.

1. Introduction

Prostate cancer is the second most common cancer in men and has an incidence rate of 16 % [1]. For prostate cancer patients undergoing radiotherapy, rectal toxicity is a significant concern. While the occurrence rates of rectal toxicities are low [2,3] some patients can endure severe and long-lasting complications, impacting their quality of life [4–6]. The understanding of mechanisms driving rectal toxicity remains incomplete [6].

Several studies explored the relationship between rectal dose and its effects on patients. Many current models used for predicting toxicity in prostate cancer radiotherapy are based on dose-volume histograms [7–11], with the disadvantage that 3D dose distributions are compressed into a single number, thereby removing the dose's spatial information [12,13]. To address this, recent research focuses on voxel-wise analysis, with the aim of finding anatomical subregions that are dose-sensitive [14–16]. For example, Hoogeman et al. [17] projected the rectal wall into a 2D map by calculating the central axis and segmenting it and Shelley et al. [18] used finite element modeling to preserve rectal anatomy and found that upper and lower rectal regions are associated with proctitis and rectal bleeding.

However, these studies encountered limitations in fully exploiting these methodologies, especially in accounting for variations in rectum length and prostate positioning across contouring protocols. Despite the promise of voxel-wise analysis, the accurate modeling of the rectum and consistent contouring remain significant challenges. The variability in rectal anatomy and inconsistencies in contouring practices have been identified as key limiting factors [17].

These limitations raise the need for consistent contouring in large multicenter studies [19,20]. Inter-Observer Variation (IOV) on the rectum and its consequence on dosimetry has been widely reported [21,22], and machine learning algorithms have been developed to automate contouring, with comparable performance to clinicians [23–26]. The main advantage of auto segmentation is consistency and lack of bias introduced by different contouring protocols and IOV [23–25]. Auto-segmentation was shown to reduce contouring and dose inconsistencies and improve outcome modelling of clinical trials [27].

In this study we aim to develop a new methodology to produce dose surface maps of the rectum which, together with auto segmented delineations, is designed to account for length differences and, therefore, maximise the inclusion of patients in the study. This method implements a novel approach to unfold and standardise the rectum, while keeping the relative position of the prostate fixed. We deploy an auto-segmentation model to standardise rectum segmentations across the large, multi-centre REQUITE dataset. We perform voxel-based analysis to identify spatial drivers of rectal surface dose and toxicity outcomes using both the automatically and clinically delineated structures [28].

2. Materials and methods

2.1. Patient cohort

The patient cohort was taken from the REQUITE study, a multicentre, international prospective study with standardised longitudinal data collection (Table 1). Data were available for 1,758 patients with prostate cancer recruited at 17 hospitals in 7 European countries and the USA, treated and followed up between April 2014 and October 2016 [29]. For each patient, planning CT scans, segmentations, planned dose distributions, and demographic information were accessible. Additionally, clinician and patient-reported outcomes were recorded, assessing toxicity levels for a minimum of two years post-radiotherapy. Clinician-reported outcomes were obtained using the Common Terminology Criteria for Adverse Events (CTCAE) scale v4.0 [30] at baseline (0 months), 1 month, 12 months, 24 months, and 36 months. Patients also reported toxicities through validated questionnaires [31] which followed the REQUITE study protocols [29]. All patients gave written informed consent. The study was approved by local ethics committees

Table 1
Clinical and demographic data for the 1,048 REQUITE prostate cancer patients that were included in the analysis. All patients were treated using external beam radiotherapy. IQR = interquartile range, PSA = prostate-specific antigen, SD = standard deviation, fx = fraction.

Clinical data for REQUITE prostate cancer patients (n = 1,048)	
Age (years)	
Median (IQR)Mean (STD)	70 (65–75)69 (7.1)
Weight (kg)	
Median (IQR)	82 (74 – 91)
Mean (STD)	83 (14)
T stage, n (%)	
T1a/T1b/T1c	260 (25 %)
T2a/T2b/T2c	424 (40 %)
T3a/T3b	131 (13 %)
T4	12 (1 %)
Not known	221 (21 %)
Gleason score, n (%)	
≤ 6	167 (16 %)
7	619 (59 %)
≥ 8	257 (25 %)
PSA (ng/ml)	
Median (IQR)	9.6 (6.6 – 16)
Mean (STD)	15.6 (22.3)
Treatment dose (Gy)	
Mean total dose (STD)	71.2 (6.8)
Median total dose (IQR)	74.0 (68.5 – 76)
Mean dose/fx (STD)	2.2 (0.4)
Median dose/fx (IQR)	2.0 (2.0–2.2)
Clinical history, n (%)	
Diabetes	145 (14 %)
Inflammatory bowel disease	31 (3 %)
Hemorrhoids	232 (22 %)
Hypertension	532 (51 %)
Previous abdominal surgery	365 (35 %)

[29].

2.2. Rectum contours

2.2.1. Automatic contours

For each patient, deep learning contours of the prostate, rectum and bladder were generated using ADMIRE® v3.4, (Elekta AB, Sweden), referred to as automatic contours. These were assumed to have better cranial-caudal consistency due to consistent contouring extent from above the anus to the start of the sigmoid. Contours created by the treating oncologist are referred to as manual contours. Automatic contours were visually inspected for gross failures.

2.2.2. Identification of manual contours

As the data in REQUITE was collected from multiple centres across 8 countries, contour naming was inconsistent and in multiple languages. To identify the correct manual rectum contours, we calculated the Sørensen–Dice similarity coefficient (SDC) [32] and the average of the absolute distances in 3D (d) between the delineation and the automatic rectum. These metrics were combined in a coefficient $\psi = \frac{d}{1+\mathrm{SDC}(V_{auto}, V)}$, in order to limit cases where the anus was identified as the rectum. The delineation with the smallest value of ψ was assumed to be the manual rectum contour. Inspection of the name of the identified delineation was conducted to confirm the accuracy of the identification.

2.2.3. Local validation of automatic contours

To validate the automatic contours, we used cylindrical mapping using the craniocaudal axis (y) as the main axis. On each transversal slice, the centre of mass (CoM) of the automatic contour was identified. Distances from the CoM to the chosen segmentation boundary (automatic or manual) were computed for 100 equidistant angles, both for the $r_{manual}(\theta, y)$ and $r_{auto}(\theta, y)$. The zero degrees angle was set at the right side of the rectum. Then, the radial distances between the automatic and manual contours were used to quantify local contour variation by defining a radial difference $\Delta r(\theta, y) = r_{manual}(\theta, y) - r_{auto}(\theta, y)$. We calculated $\Delta r(\theta, y)$ for each slice and angle of the automatic rectum delineation resulting in ΔR maps. ΔR maps had a variable number of rows (corresponding to the number of slices of the automatic rectum) and a fixed number of columns (corresponding to 100 angles). Since the automatic rectum contour was used as a reference, there were slices where voxels had an undefined $r_{manual}(\theta, y)$. In these cases, $\Delta r(\theta, y)$ were set to a NaN.

We calculated and reported statistics on the contour variation. For the analysis, we included only the subset of patients whose contour variation did not exceed ± 3 mm for all voxels, ensuring consistency between manual and automatic rectum contours.

2.3. Surface dose mapping and standardisation of the rectum length

To map the rectal surface dose, we used the cylindrical mapping described above. Instead of populating the maps with radial differences, we sampled the planned radiotherapy dose at these angles and distances to produce a 2D dose surface map.

A coordinate transformation was applied to the surface maps, allowing all maps to be transformed to a standard length, arbitrarily chosen to be 61 slices, see Fig. 1. The CoM of the automatic prostate served as the origin. For a rectum extending between a and b (cranial to caudal extent), slices in the upper half were linearly transformed from (prostate CoM, a], to (0, 30]. Similarly, the slices in the bottom half of the rectum were transformed from [b, prostate CoM), to [-30, 0) using a second linear transformation. This method assumed that the anatomical structure of the rectum can be aligned relative to the prostate and is the same for shorter and longer rectum contours.

This process resulted in a map of 61 slices and was applied to both the dose and contour variation data. The physical dose was converted to biologically effective dose (BED) using $\alpha/\beta = 3$ Gy [33]. We calculated and reported the variation in linear scaling across patients for the upper and lower half of the automatic rectum.

2.4. Statistical analysis

All non-baseline toxicities were analysed, including clinician-reported proctitis, rectal bleeding, diarrhoea, and patient-reported bowel pain, constipation, bowel urgency, diarrhoea, and bowel control (Table 2). Endpoints with less than 5 % event cases were excluded.

We used two methodologies for 2D voxel-wise analysis: (1) a two-tailed Student's t-test for binary analysis with the highest-reported toxicities dichotomised to grade < 2 and ≥ 2 as this is of clinical significance [30]; (2) Cox Proportional Hazards Model (CPHM) for time-to-event analysis [34]. The time to event was chosen to be time to the

Table 2
Event cases until maximum of 3-years post radiotherapy for various toxicity endpoints of the 1,048 REQUITE prostate cancer patients that were included in the analysis.

Clinical endpoint	Grading system	Incidence n (%)
Proctitis ≥ Grade 2	CTCAE	137 (13 %)
Diarrhoea ≥ Grade 2	CTCAE	89 (8 %)
Rectal bleeding ≥ Grade 2	CTCAE	61 (6 %)
Sphincter control ≥ Grade 2	CTCAE	12 (1 %)
Bowel urgency ≥ Grade 2	Patient-reported	640 (61 %)
Diarrhoea ≥ Grade 2	Patient reported	71 (7 %)
Bowel control ≥ Grade 2	Patient-reported	153 (15 %)
Pain bowels ≥ Grade 2	Patient-reported	156 (15 %)

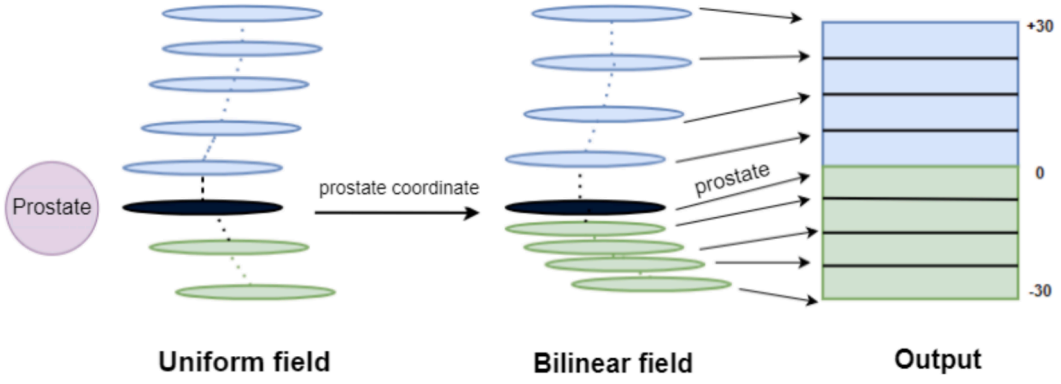

Fig. 1. Schematic diagram showing the coordinate transformation process of a rectum contour to a standardised length of 61 slices using two linear transformations and interpolation on the top half and bottom half of the rectum. The centre of mass (CoM) of the automatic prostate coordinate in the craniocaudal direction is chosen as the origin point and the process results in a bilinear field after following the height standardisation methodology described.

highest reported toxicity (worst scoring event) excluding the baseline toxicity. The CPHM analysis has two main advantages: it includes clinical variables through multivariable voxel-based analysis and accounts for time-to-event. Covariates tested in our study included patient age, as well as rectal and prostate volumes, both derived from the automatic contours. The CPHM analysis yielded multi-channel images, with each channel representing hazard ratios of the observed data for a given covariate [34].

Statistical significance per voxel was assessed via permutation testing to account for multiple comparisons due to its non-parametric nature [35,36], using the methodology described by Green *et al.* [34]. For CPHM, the outcome labels, survival times and covariates were permuted 1,000 times to preserve computational efficiency while retaining low confidence level uncertainty [35]. The max hazard ratio across the image was calculated to summarise each permutation. The 95th percentile of max hazard ratios was set as the significance threshold ($p < 0.05$), which was then used to threshold the real hazard ratio map and identify regions associated with the outcome. The same procedure was followed for the Student's *t*-test to find the significance value from the distribution of max t-statistics.

3. Results

3.1. Local validation of automatic contours

Files for automatic contouring were unavailable for 210 patients. Another 103 patients were excluded due to failed automatic prostate contouring, while 68 were removed for misidentified manual rectum contours. Additionally, 84 patients that received brachytherapy treatment after External Beam Radiotherapy (EBRT) were excluded as the full rectal dose could not be reconstructed. Fig. 2 shows the contour variation quantification results, with the mean variation of the voxel-wise maps for the mean ΔR centered around $\mu = -0.3$ mm (Fig. 2(a)). 95.9 % of patients had a mean contour variation within $\pm$ 3 mm, Fig. 2 (c). There were patients for which the two contours were inconsistent, leading to slices in which their variation exceeded 5 mm (Supp. Material 1). 245 patients were removed due to voxels with contour variation exceeding $\pm$ 3 mm, to ensure sufficient agreement between manual and automatic contours, leaving 1,048 patients for the final analysis. A flowchart illustrating the data pre-processing is available in Supplementary Material 2.

For 818 patients the manual rectum contour was shorter than the automatic contour, in either the caudal or cranial direction, corresponding to patients with NaN values in the dose surface maps for the manual rectum.

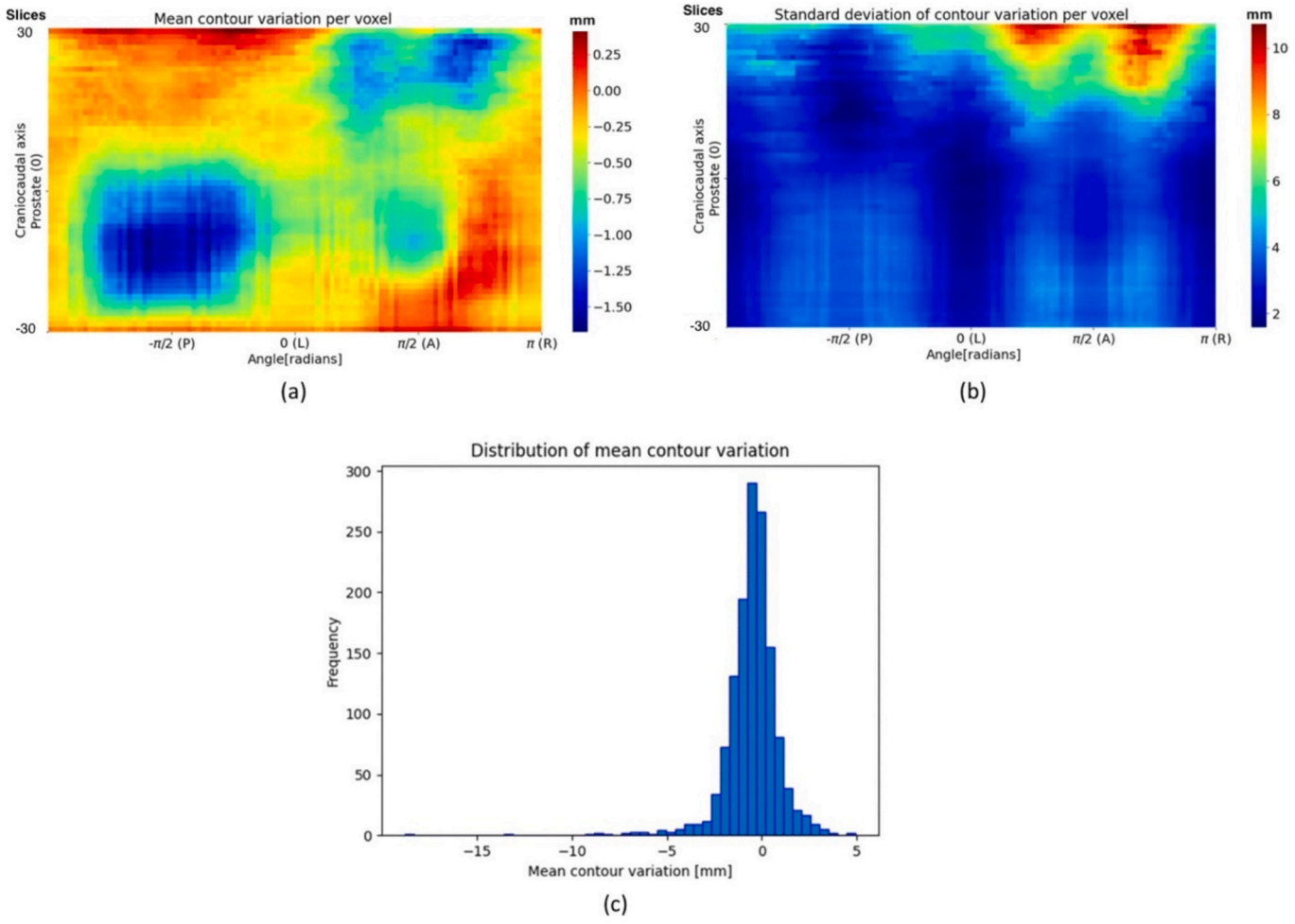

Fig. 2. Contour variation quantification. Voxel-wise (a) mean and (b) standard deviation summaries for ΔR for n = 1,273 and (c) histogram showing frequency of average contour variation of all voxels for a given patient. The mean of all voxels in (a) is very close to 0 (−0.3 mm) and there are two clusters for which the mean ΔR is < -1 mm. The standard deviation remained relatively small in the whole region of the rectum apart from the upper anterior region. The large deviation is due to some erroneous patients for which the manual rectum contour was not consistent with the automatic contour, leading to extreme variations. This deviation is also observed in the long negative tail in (c).

The standard deviation of the scaling across patients for the lower half of the rectum was 0.28 while for the upper half of the rectum was 0.37.

3.2. Student's t-test results

Fig. 3 shows the two-tailed Student's *t*-test results using the dose surface maps of the automatic and manual contours. Significance ($p < 0.05$) was found for clinician-reported proctitis and patient-reported bowel urgency, with no significance for other toxicities. For both endpoints, the 95 % significance region included the lower posterior. Small regions in the upper and lower anterior, as well as the upper posterior, also showed significance for bowel urgency, however these had high dose standard deviation (see Supp. Material 3). Significant regions corresponded to the lower tail of the *t*-test, indicating that higher doses in these areas increase toxicity risk. The negative t-value regions suggest a higher mean dose for the event group (see Supp. Material 4). Similar spatial locations were identified for the manual contours, but the significant regions were smaller, see Fig. 3.

3.3. CPHM results

Results of the univariable voxel-wise CPHM analysis are shown in Fig. 4. Significance ($p < 0.05$) was found in the lower posterior for clinician-reported proctitis using automatic contours, indicating 3 % increased risk per Gy. Patient-reported bowel urgency was significant in the lower posterior for both the automatic and manual contours suggesting approximately 2 % increased risk per Gy, see Fig. 4. No other endpoints showed significance. The multivariable voxel-wise CPHM analysis results were consistent with the univariable analysis (Supp. Material 5).

4. Discussion

This study introduces a novel method for standardising the rectum length and projecting the rectum into 2D surface maps while maintaining the prostate's relative position. Consistent delineation of rectal anatomy was achieved using deep-learning auto-segmentation. Analysis of 1,048 patients revealed an association between higher planned doses in the lower posterior and increased risk of proctitis and bowel urgency. This methodology offers the advantage to map anatomical locations consistently across patients and study the entire length of the rectum. Without linear rescaling, the analysis would not have accounted for individual anatomical variations in a comparable way.

Our study used the large prospective multicenter REQUITE data, which captures the diversity of treatment deliveries, segmentation protocols and patient demographics, allowing for greater generalisability compared to smaller, single-center studies. Previous studies have demonstrated correlation between toxicity and dose at the lower rectum [15,18,37–39]. Huang *et al.* [40], and Jackson *et al.* [41] conducted dose-volume histogram analysis and showed that rectal complications increase with higher irradiated volume, while Cho *et al.* [42] identified a correlation between dose at the rectal posterior and higher risk of proctitis. These studies, however, did not account for 3D anatomy. A study by Onjukka *et al.* [37] demonstrated a link between higher doses at the posterior rectum and rectal bleeding using a voxel-wise analysis. Shelley *et al.* [18] investigated the relationship between voxel-level dose and rectal toxicity and identified significant regions in the lower posterior for rectal bleeding and proctitis. The methodologies in these studies did not account for the variable rectal length and the relative prostate position and, additionally, Shelley *et al.* [18] faced limitations due to small sample size. Shelley's investigation differed in toxicity rates, patient treatment, and dose evaluation method, as it focused on patients undergoing image-guided intensity modulated radiotherapy (IG-IMRT) and employed accumulated rather than planned dose. Despite variations in methods, sample sizes and limitations, we find our study consistent with the findings of Shelley *et al.* [18] and Onjukka *et al.* [37] for proctitis.

While our findings agree with previous research findings [18,37], voxel-based analysis has limitations due to the inherent spatial correlation of the dose [43]. Because of this, we cannot rule out the importance of other regions other than the posterior. The derived region presented in this work is purely statistical and not clinically derived, however it provides guidance on generating meaningful hypotheses to be tested in future clinical studies. The lack of significance in the anterior region could be attributed to the lack of dose variation, since all patients received high doses in the region closest to the tumour. Validation in further cohorts is needed before any clinical translation studies.

Using manual rectum contours introduces limitations due to

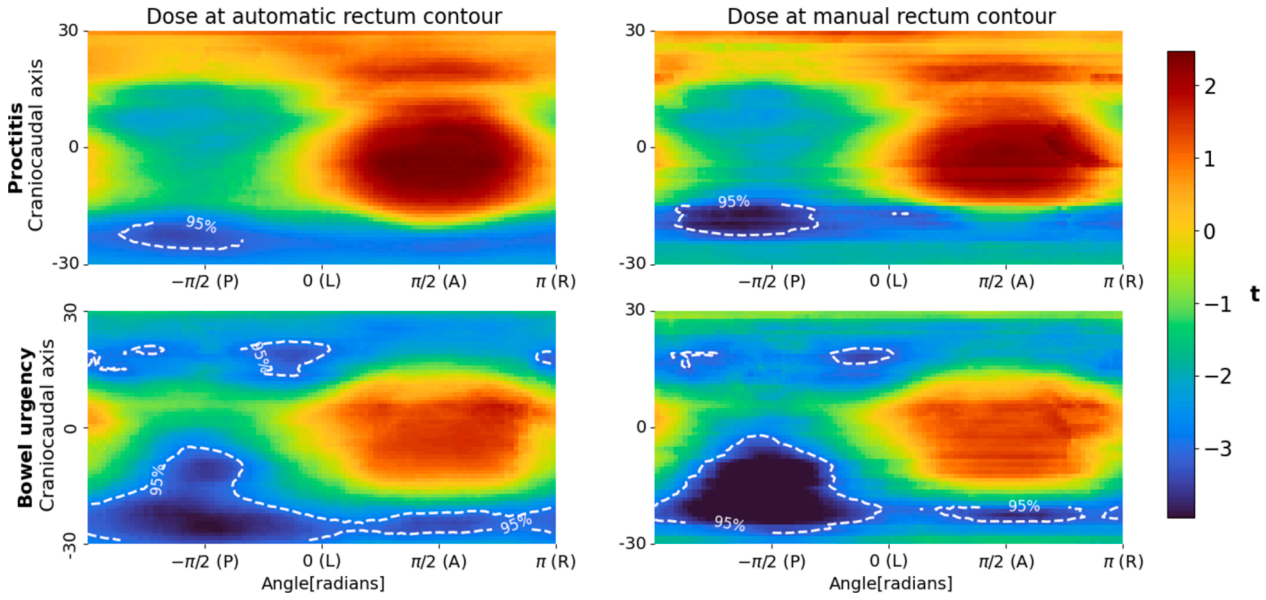

Fig. 3. Four surface maps showing the output distribution values from Student's t-tests for 1,048 patients, with regions of 95% significance outlined. The top two maps illustrate the significant regions for proctitis, comparing the dose at the manual rectum (right) versus the automatic rectum (left). The bottom two maps show the same comparison for bowel urgency. Results suggest that reducing the dose in the significant regions could be beneficial for the outcome.

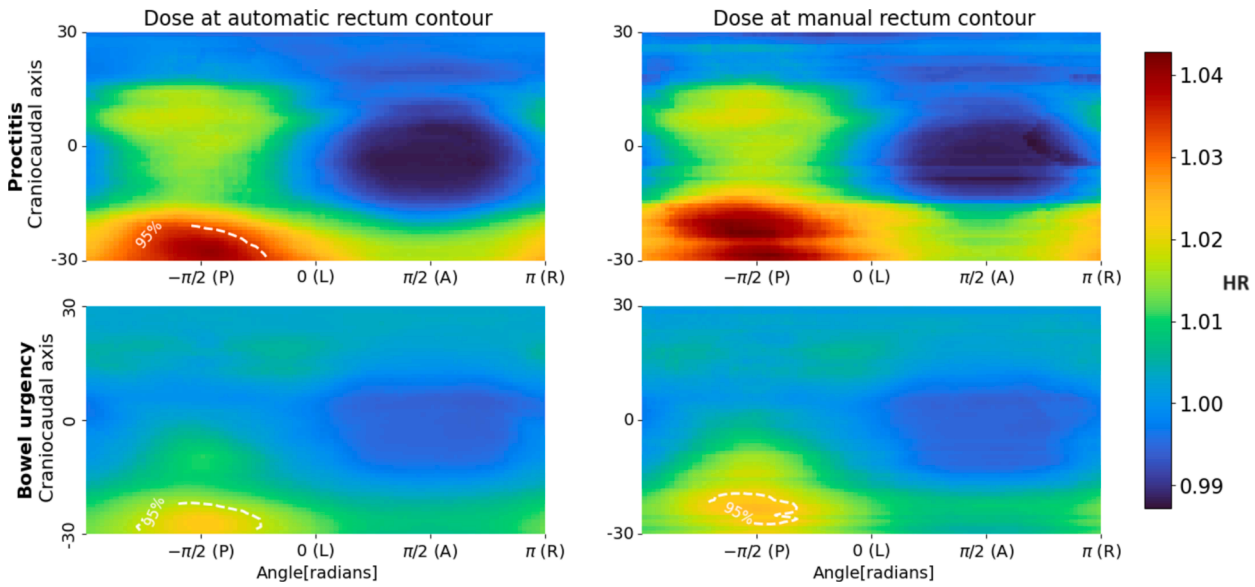

Fig. 4. Four hazard ratio maps from univariable Cox Proportional Hazards Model (CPHM) analysis performed on 1,048 patients, with regions of 95% significance outlined. The top two maps illustrate the significant regions for proctitis, comparing the dose at the manual rectum (right) versus the automatic rectum (left). The bottom two maps show the same comparison for bowel urgency. For proctitis using the automatic dose, results suggest a risk increase of 3.3–4.0% per Gy increase in dose. For bowel urgency, a risk increase of 1.8–2.2% per Gy increase in dose is observed for the automatic dose, whereas for the manual dose the risk increase is 2.1–2.4%.

inconsistent lengths influenced by local segmentation protocols. Among 1,048 patients, 818 had shorter manual rectum contours than automatic ones, which would make standardisation challenging without the automatic segmentations. In this context, automatic contours provide a more consistent baseline for analysis. However, the method of standardising the rectum assumed that rectal anatomy relative to the prostate is independent of the rectum length, which may not be entirely accurate.

Despite near-zero mean contour variation indicating strong agreement, the lower posterior showed the highest negative mean variation (Fig. 2), likely reflecting contouring challenges or protocol differences in the region. The regions of significance found by the Student's *t*-test for proctitis and bowel urgency using the dose at the manual rectum were predominantly smaller, suggesting that the analysis for the manual rectum may be limited by the inconsistent cranio-caudal extension of the rectum. This observation is further supported by the CPHM analysis, which showed significance for proctitis when using the automatic contours, while no significant findings were observed for the manual rectum. The differences in results between the Student's *t*-test and the CPHM analysis could be attributed to the fact that one is a binary analysis while the other is a time-to-event analysis. Both methodologies, however, highlight similar regions which strengthens our results.

Sripadam *et al.* [44] showed that rectal volume can decrease during treatment. Similarly, van Herk *et al.* [45] identified rectal filling as a significant contributor to prostate motion, while Stasi *et al.* [10] observed rectal volume variation between planning and treatment. These studies highlight the discrepancy between planned and delivered doses due to rectal motion, which is a limitation of this study. Multiple studies support that using delivered doses can yield more accurate predictions [18,46,47]. Shelley *et al.* [18] found larger significant regions for the accumulated dose, suggesting that certain rectal regions may be missed with the planned dose, however improvements were small. Scaife *et al.* [48] found that the delivered doses were generally lower than planned doses, though their analysis was limited by insufficient scan coverage of the lower rectum. In our study, the lack of delivered dose data prevented an assessment of rectal motion and the impact of accumulated dose on treatment outcomes.

Current clinical practices increasingly adopt spacers, which have shown to reduce the mean rectal doses and reduce rectal toxicities [49]. Spacers could reduce doses in the lower posterior, which is the region of interest in this study. However, rectal spacers were not used in this study, so their impact could not be estimated.

Finally, studies have shown that dose to pelvic floor muscles, including the internal and external anal sphincter as well as the puborectalis muscles surrounding the rectum, correlates with toxicity endpoints such as urgency and fecal incontinence [50–52]. An in-depth analysis of rectal toxicities should combine dose surface mapping with anatomical mapping using image registration as done in studies of prostate cancer [16] and lung cancer [53].

This study has found that the lower region of the rectum can be important in predicting certain dose related side effects in prostate cancer radiotherapy, supporting previous findings. However, the region often has variations in contouring and may be overlooked with local segmentation protocols, leading to suboptimal treatment planning and outcomes.

To summarise, our study quantified rectal doses for 1,048 prostate cancer patients in the REQUITE dataset using deep-learning auto-segmentation. A novel method standardised and unfolded the rectum while keeping the prostate fixed, which allowed to project the dose distribution into a 2D surface map. Statistical analysis revealed a significant region in the lower posterior ($p < 0.05$) associated with clinician-reported proctitis and patient-reported bowel urgency. Reducing the dose in this area could lower toxicity risk, highlighting opportunities for optimising treatment and improving patient care.

CRediT authorship contribution statement

Artemis Bouzaki: Methodology, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing, Software. **Dylan Green:** Investigation, Writing – review & editing. **Marcel van Herk:** Conceptualization, Resources, Writing – review & editing, Funding acquisition. **Jane Shortall:** Writing – review & editing. **Tanuj Puri:** Writing – review & editing. **Sarah Kerns:** Data curation, Writing – review & editing. **David Azria:** Data curation, Writing – review & editing. **Marrie-Pierre Farcy-Jacquet:** Data curation, Writing – review & editing. **Jenny Chang-Claude:** Data curation, Writing – review & editing. **Ananya Choudhury:** Data curation, Writing – review &

editing. **Alison Dunning:** Data curation, Writing – review & editing. **Maarten Lambrecht:** Data curation, Writing – review & editing. **Barbara Avuzzi:** Data curation, Writing – review & editing. **Dirk De Ruysscher:** Funding acquisition, Writing – review & editing. **Petra Seibold:** Data curation, Writing – review & editing. **Elena Sperk:** Data curation, Writing – review & editing. **Christopher Talbot:** Data curation, Writing – review & editing. **Ana Vega:** Data curation, Writing – review & editing. **Liv Veldeman:** Data curation, Writing – review & editing. **Adam Webb:** Data curation, Writing – review & editing. **Barry Rosenstein:** Data curation, Writing – review & editing. **Catharine M. West:** Data curation, Writing – review & editing. **Eliana Gioscio:** Data curation, Writing – review & editing. **Tiziana Rancati:** Data curation, Writing – review & editing. **Eliana Vasquez Osorio:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing, Project administration, Resources, Supervision. **Alan McWilliam:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing, Project administration, Resources, Supervision, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

REQUITE received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 601826. Dr Alan McWilliam Profs A Choudhury, C Faivre-Finn and C West are supported by NIHR Manchester Biomedical Research Centre and by Cancer Research UK via funding to the Cancer Research Manchester Centre [C147/A25254and by the Cancer Research UK RadNet Manchester [C1994/A28701]. Dr Deborah Marshall is supported by the Office Of The Director, National Institutes Of Health under Award Number DP50D031876. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr Tim Rattay and Prof Christopher Talbot are supported by the NIHR Leicester Biomedical Research Centre. Sara Gutiérrez-Enríquez is supported by the Government of Catalonia (2021SGR01112). Vall d'Hebron Institute of Oncology (VHIO) acknowledge the Cellex Foundation for providing research facilities, the CERCA Programme/Generalitat de Catalunya for institutional support, and the Agencia Estatal de Investigación for their financial support as a Center of Excellence Severo Ochoa (CEX2020-001024-S/AEI/10.13039/501100011033). Ana Vega is supported by Spanish Instituto de Salud Carlos III (ISCIII) funding, an initiative of the Spanish Ministry of Economy and Innovation partially supported by European Regional Development FEDER Funds (PI22/00589, PI19/01424; INT20/00071); the ERAPerMed JTC2018 funding (AC18/00117); the Autonomous Government of Galicia (Consolidation and structuring program: IN607B), and by the AECC (PRYES211091VEGA).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2025.100701.

References

[1] National Cancer Institute. SEER Cancer Statistics Review, 1975-2013. Https://SeerCancerGov/Csr/1975_2015/ 2016.
[2] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047–60. https://doi.org/10.1016/S1470-2045(16)30102-4.
[3] Tree AC, Ostler P, van der Voet H, Chu W, Loblaw A, Ford D, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23:1308–20. https://doi.org/10.1016/S1470-2045(22)00517-4.
[4] Hauer-Jensen M, Wang J, Boerma M, Fu Q, Denham JW. Radiation damage to the gastrointestinal tract: mechanisms, diagnosis, and management. Curr Opin Support Palliat Care 2007;1:23–9. https://doi.org/10.1097/SPC.0b013e3281108014.
[5] Sebastian S, O'Connor H, O'Morain C, Buckley M. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. J Gastroenterol Hepatol 2004;19:1169–73. https://doi.org/10.1111/j.1440-1746.2004.03448.x.
[6] Barnett GC, West CML, Dunning AM, Elliott RM, Coles CE, Pharoah PDP, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009;9:134–42. https://doi.org/10.1038/nrc2587.
[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. https://doi.org/10.1200/JCO.2009.25.8475.
[8] Fiorino C, Cozzarini C, Vavassori V, Sanguineti G, Bianchi C, Mauro Cattaneo G, et al. Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. Radiother Oncol 2002;64:1–12. https://doi.org/10.1016/S0167-8140(02)00147-0.
[9] Fiorino C, Sanguineti G, Cozzarini C, Fellin G, Foppiano F, Menegotti L, et al. Rectal dose–volume constraints in high-dose radiotherapy of localized prostate cancer. International Journal of Radiation Oncology*Biology*Physics 2003;57:953–62. https://doi.org/10.1016/S0360-3016(03)00665-5.
[10] Stasi M, Munoz F, Fiorino C, Pasquino M, Baiotto B, Marini P, et al. Emptying the rectum before treatment delivery limits the variations of rectal dose–volume parameters during 3DCRT of prostate cancer. Radiother Oncol 2006;80:363–70. https://doi.org/10.1016/J.RADONC.2006.08.007.
[11] Someya M, Hori M, Tateoka K, Nakata K, Takagi M, Saito M, et al. Results and DVH analysis of late rectal bleeding in patients treated with 3D-CRT or IMRT for localized prostate cancer. J Radiat Res 2015;56:122–7. https://doi.org/10.1093/jrr/rru080.
[12] Sosa-Marrero C, Acosta O, Pasquier D, Thariat J, Delpon G, Fiorino C, et al. Voxel-wise analysis: a powerful tool to predict radio-induced toxicity and potentially perform personalised planning in radiotherapy. Cancer/Radiothérapie 2023;27:638–42. https://doi.org/10.1016/j.canrad.2023.06.024.
[13] Sanchez-Nieto B, et al. Biological dose surface maps: evaluation of 3D dose data for tubular organs. Radiother Oncol 2001;61.
[14] Chen B, Acosta O, Kachenoura A, Ospina JD, Dréan G, Simon A, et al. Spatial characterization and classification of rectal bleeding in prostate cancer radiotherapy with a voxel-based principal components analysis model for 3D dose. Distribution 2011:60–9. https://doi.org/10.1007/978-3-642-23944-1_7.
[15] Dréan G, Acosta O, Lafond C, Simon A, de Crevoisier R, Haigron P. Interindividual registration and dose mapping for voxelwise population analysis of rectal toxicity in prostate cancer radiotherapy. Med Phys 2016;43:2721–30. https://doi.org/10.1118/1.4948501.
[16] Acosta O, Drean G, Ospina JD, Simon A, Haigron P, Lafond C, et al. Voxel-based population analysis for correlating local dose and rectal toxicity in prostate cancer radiotherapy. Phys Med Biol 2013;58:2581–95. https://doi.org/10.1088/0031-9155/58/8/2581.
[17] Hoogeman MS, van Herk M, de Bois J, Muller-Timmermans P, Koper PCM, Lebesque JV. Quantification of local rectal wall displacements by virtual rectum unfolding. Radiother Oncol 2004;70:21–30. https://doi.org/10.1016/j.radonc.2003.11.015.
[18] Shelley LEA, Sutcliffe MPF, Thomas SJ, Noble DJ, Romanchikova M, Harrison K, et al. Associations between voxel-level accumulated dose and rectal toxicity in prostate radiotherapy. Phys Imaging Radiat Oncol 2020;14:87–94. https://doi.org/10.1016/j.phro.2020.05.006.
[19] Njeh CF. Tumor delineation: the weakest link in the search for accuracy in radiotherapy. J Med Phys 2008;33:136–40. https://doi.org/10.4103/0971-6203.44472.
[20] Vanherk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52–64. https://doi.org/10.1053/j.semradonc.2003.10.003.
[21] Gual-Arnau X, Ibáñez-Gual MV, Lliso F, Roldán S. Organ contouring for prostate cancer: Interobserver and internal organ motion variability. Comput Med Imaging Graph 2005;29:639–47. https://doi.org/10.1016/j.compmedimag.2005.06.002.
[22] Chicas-Sett R, Celada-Alvarez F, Roldan S, Rodriguez-Villalba S, Santos-Olias M, Soler-Catalan P, et al. Interobserver variability in rectum contouring in high-dose-rate brachytherapy for prostate cancer: a multi-institutional prospective analysis. Brachytherapy 2018;17:208–13. https://doi.org/10.1016/j.brachy.2017.09.015.
[23] Liu Z, Liu X, Guan H, Zhen H, Sun Y, Chen Q, et al. Development and validation of a deep learning algorithm for auto-delineation of clinical target volume and organs at risk in cervical cancer radiotherapy. Radiother Oncol 2020;153:172–9. https://doi.org/10.1016/j.radonc.2020.09.060.
[24] Lin L, Dou Q, Jin Y-M, Zhou G-Q, Tang Y-Q, Chen W-L, et al. Deep learning for automated contouring of primary tumor volumes by MRI for nasopharyngeal carcinoma. Radiology 2019;291:677–86. https://doi.org/10.1148/radiol.2019182012.
[25] Jin D, Guo D, Ge J, Ye X, Lu L. Towards automated organs at risk and target volumes contouring: defining precision radiation therapy in the modern era. Journal of the National Cancer Center 2022;2:306–13. https://doi.org/10.1016/j.jncc.2022.09.003.

[26] Cardenas CE, Yang J, Anderson BM, Court LE, Brock KB. Advances in auto-segmentation. Semin Radiat Oncol 2019;29:185–97. https://doi.org/10.1016/j.semradonc.2019.02.001.
[27] Thor M, Apte A, Haq R, Iyer A, LoCastro E, Deasy JO. Using auto-segmentation to reduce contouring and dose inconsistency in clinical trials: the simulated impact on RTOG 0617. International Journal of Radiation Oncology*Biology*Physics 2021;109:1619–26. https://doi.org/10.1016/j.ijrobp.2020.11.011.
[28] Jenkins A, Mullen TS, Johnson-Hart C, Green A, McWilliam A, Aznar M, et al. Novel methodology to assess the effect of contouring variation on treatment outcome. Med Phys 2021;48:3234–42. https://doi.org/10.1002/mp.14865.
[29] Seibold P, Webb A, Aguado-Barrera ME, Azria D, Bourgier C, Brengues M, et al. REQUITE: a prospective multicentre cohort study of patients undergoing radiotherapy for breast, lung or prostate cancer. Radiother Oncol 2019;138:59–67. https://doi.org/10.1016/j.radonc.2019.04.034.
[30] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Https://CtepCancerGov/Protocoldevelopment/Electronic_applications/Docs/Ctcae_v5_quick_reference_85x11Pdf 2017.
[31] Farnell DJJ, Mandall P, Anandadas C, Routledge J, Burns MP, Logue JP, et al. Development of a patient-reported questionnaire for collecting toxicity data following prostate brachytherapy. Radiother Oncol 2010;97:136–42. https://doi.org/10.1016/j.radonc.2010.05.011.
[32] Johnson LL, Shih JH. An introduction to survival analysis. Principles and practice of clinical research. Elsevier 2007:273–82. https://doi.org/10.1016/B978-012369440-9/50024-4.
[33] Jones B, Dale RG, Deehan C, Hopkins KI, Morgan DAL. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol 2001;13:71–81. https://doi.org/10.1053/clon.2001.9221.
[34] Green A, Vasquez Osorio E, Aznar MC, McWilliam A, van Herk M. Image based data mining using per-voxel cox regression. Front Oncol 2020;10:1178. https://doi.org/10.3389/fonc.2020.01178.
[35] Palma G, Monti S, Cella L. Voxel-based analysis in radiation oncology: a methodological cookbook. Phys Med 2020;69:192–204. https://doi.org/10.1016/j.ejmp.2019.12.013.
[36] Bennett C, Miller M, Wolford G. Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: an argument for multiple comparisons correction. Neuroimage 2009;47:S125. https://doi.org/10.1016/S1053-8119(09)71202-9.
[37] Onjukka E, Fiorino C, Cicchetti A, Palorini F, Improta I, Gagliardi G, et al. Patterns in ano-rectal dose maps and the risk of late toxicity after prostate IMRT. Acta Oncol (Madr) 2019;58:1757–64. https://doi.org/10.1080/0284186X.2019.1635267.
[38] Vanneste BGL, Buettner F, Pinkawa M, Lambin P, Hoffmann AL. Ano-rectal wall dose-surface maps localize the dosimetric benefit of hydrogel rectum spacers in prostate cancer radiotherapy. Clin Transl Radiat Oncol 2019;14:17–24. https://doi.org/10.1016/j.ctro.2018.10.006.
[39] Stenmark MH, Conlon ASC, Johnson S, Daignault S, Litzenberg D, Marsh R, et al. Dose to the inferior rectum is strongly associated with patient reported bowel quality of life after radiation therapy for prostate cancer. Radiother Oncol 2014;110:291–7. https://doi.org/10.1016/j.radonc.2014.01.007.
[40] Huang EH, Pollack A, Levy L, Starkschall G, Dong L, Rosen I, et al. Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. International Journal of Radiation Oncology*Biology*Physics 2002;54:1314–21. https://doi.org/10.1016/S0360-3016(02)03742-2.
[41] 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. International Journal of Radiation Oncology*Biology*Physics 2001;49:685–98. https://doi.org/10.1016/S0360-3016(00)01414-0.
[42] Cho KH, Lee CK, Levitt SH. Proctitis after conventional external radiation therapy for prostate cancer: importance of minimizing posterior rectal dose. Radiology 1995;195:699–703.
[43] McWilliam A, Palma G, Abravan A, Acosta O, Appelt A, Aznar M, et al. Voxel-based analysis: roadmap for clinical translation. Radiother Oncol 2023;188:109868. https://doi.org/10.1016/j.radonc.2023.109868.
[44] Sripadam R, Stratford J, Henry AM, Jackson A, Moore CJ, Price P. Rectal motion can reduce CTV coverage and increase rectal dose during prostate radiotherapy: a daily cone-beam CT study. Radiother Oncol 2009;90:312–7. https://doi.org/10.1016/j.radonc.2008.07.031.
[45] van Herk M, Bruce A, Guus Kroes AP, Shouman T, Touw A, Lebesque JV. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. International Journal of Radiation Oncology*Biology*Physics 1995;33:1311–20. https://doi.org/10.1016/0360-3016(95)00116-6.
[46] Shelley LEA, Scaife JE, Romanchikova M, Harrison K, Forman JR, Bates AM, et al. Delivered dose can be a better predictor of rectal toxicity than planned dose in prostate radiotherapy. Radiother Oncol 2017;123:466–71. https://doi.org/10.1016/j.radonc.2017.04.008.
[47] Swaminath A, Massey C, Brierley JD, Dinniwell R, Wong R, Kim JJ, et al. Accumulated delivered dose response of stereotactic body radiation therapy for liver metastases. International Journal of Radiation Oncology*Biology*Physics 2015;93:639–48. https://doi.org/10.1016/j.ijrobp.2015.07.2273.
[48] Scaife JE, Thomas SJ, Harrison K, Romanchikova M, Sutcliffe MPF, Forman JR, et al. 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. Br J Radiol 2015;88:20150243. https://doi.org/10.1259/bjr.20150243.
[49] Pinkawa M, Klotz J, Djukic V, Schubert C, Escobar-Corral N, Caffaro M, et al. Learning curve in the application of a hydrogel spacer to protect the rectal wall during radiotherapy of localized prostate cancer. Urology 2013;82:963–8. https://doi.org/10.1016/j.urology.2013.07.014.
[50] Smeenk RJ, Hoffmann AL, Hopman WPM, van Lin ENJT, Kaanders JHAM. Dose-effect relationships for individual pelvic floor muscles and anorectal complaints after prostate radiotherapy. International Journal of Radiation Oncology*Biology*Physics 2012;83:636–44. https://doi.org/10.1016/j.ijrobp.2011.08.007.
[51] Buettner F, Gulliford SL, Webb S, Sydes MR, Dearnaley DP, Partridge M. The dose–response of the anal sphincter region – an analysis of data from the MRC RT01 trial. Radiother Oncol 2012;103:347–52. https://doi.org/10.1016/j.radonc.2012.03.002.
[52] Thor M, Olsson CE, Oh JH, Petersen SE, Alsadius D, Bentzen L, et al. Relationships between dose to the gastro-intestinal tract and patient-reported symptom domains after radiotherapy for localized prostate cancer. Acta Oncol (Madr) 2015;54:1326–34. https://doi.org/10.3109/0284186X.2015.1063779.
[53] Palma G, Monti S, Pacelli R, Liao Z, Deasy JO, Mohan R, et al. Radiation pneumonitis in thoracic cancer patients: multi-center voxel-based analysis. Cancers (Basel) 2021;13:3553. https://doi.org/10.3390/cancers13143553.