Modelling urinary dysfunction following external beam radiotherapy of the prostate based on bladder dose-surface maps: evidence of spatially-variable response of the bladder surface

Noorazrul Yahya^{1,2} MSc
Martin A Ebert^{1,3} PhD
Michael J House¹ PhD
Angel Kennedy³ BSc
John Matthews⁴ FRANZCR
David J Joseph^{3,5} FRANZCR
James W Denham⁶ FRANZCR

¹ School of Physics, University of Western Australia, Western Australia, Australia

² School of Health Sciences, National University of Malaysia, Malaysia

³ Department of Radiation Oncology, Sir Charles Gairdner Hospital, Western Australia, Australia

⁴ Department of Radiation Oncology, Auckland City Hospital, Auckland, New Zealand

⁵ School of Surgery, University of Western Australia, Western Australia, Australia

⁶ School of Medicine and Public Health, University of Newcastle, New South Wales, Australia

Number of figures: 2

Supplementary materials: 3

Number of words prior to blinding: 3489

Correspondence address:

Noorazrul Yahya
School of Physics
University of Western Australia
Stirling Hwy
Crawley, Western Australia 6009
Tel: +618 9346 4931

Email: noorazrul.yahya@research.uwa.edu.au

Running Title: Dose-surface maps & urinary dysfunction

Keywords: prostate radiotherapy, normal tissue complications, urinary dysfunction, dose-surface maps

CONFLICTS OF INTEREST NOTIFICATION

None.

SUMMARY

In a cohort of 754 patients treated with external beam radiotherapy to the prostate, we sought to examine the relationship between the spatial dose distribution to the bladder surface and symptoms of urinary dysfunction. A spatially-variable response of the bladder surface was found.

ABSTRACT

Background and Purpose: We assessed the association of the spatial distribution of dose to the bladder surface, described using dose-surface maps, with the risk of urinary dysfunction.

Materials/Methods: The bladder dose-surface maps of 754 participants from the TROG 03.04-RADAR trial were generated from the volumetric data by virtually cutting the bladder at the sagittal slice intersecting the bladder centre-of-mass through to bladder posterior and projecting the dose information on a two-dimensional plane. Pixel-wise dose comparisons between patients with and without symptoms (dysuria, haematuria, incontinence and increase of ≥ 10 International Prostate Symptom Score (Δ IPSS10)) were performed and results with and without permutation-based multiple-comparison adjustments reported. Pixel-wise multivariate analyses (peak-event model for dysuria, haematuria and Δ IPSS10; event-count model for incontinence) with adjustments for clinical factors were also reported.

Results: The associations of the spatially-specific dose measures to urinary dysfunction were found to be dependent on specific symptoms. Doses received by the anterior-inferior and, to a lesser extent, the posterior-superior surface of the bladder were found to have the strongest relationship to the incidence of dysuria, haematuria and Δ IPSS10, both with and without adjustment for clinical factors. For doses to the posterior-inferior region corresponding to the area of the trigone, the only symptom showing a significant association was incontinence.

Conclusions: Spatially variable response of the bladder surface to dose was found for symptoms of urinary dysfunction. Limiting the dose extending anteriorly may help to reduce risks.

INTRODUCTION

Dose-volume or dose-surface histograms are commonly utilised to estimate the risk of urinary dysfunction and to quantitatively describe the response of an organ to different dose distributions. An obvious limitation of analysis based on such histograms is the lack of information on the spatial distribution of the dose. To address this, the association of spatial dose distributions to specific endpoints have been studied through the use of dose-surface maps (e.g. [1-5]). For hollow organs, the maps are a two-dimensional representation of the dose planned to the organ surface, allowing dose-symptom associations in specific anatomical regions to be explicitly assessed. In the domain of urinary symptoms, the use of dose-surface maps has only recently received further attention [6].

Symptom-specific associations to dose distribution have been demonstrated for urinary symptoms. Global symptoms, like increased urinary frequency, are likely associated with the dose distribution across the whole bladder (i.e. mean dose) while associations with dysuria, haematuria and incontinence were shown to be more localised, dependent on the area of the bladder receiving high dose [7, 8]. For the former, consideration of the spatial dose distribution is potentially of little value and a dose-surface histogram is sufficient [7]. For the latter, the spatial dose distribution may add significant additional information for predicting an increased risk for specific patients, allowing discernment between planned distributions that may have differing spatial distributions which yield similar histograms.

A number of studies have investigated the relationships between localised anatomical structures of the bladder and symptoms of urinary dysfunction [6, 9, 10]. Heemsbergen et al. studied the spatial dose distribution focusing on the approximate location of the bladder trigone and urinary obstruction [9]. Ghadjar et al. delineated the distal ends of both ureters to produce dose-volume histograms of the trigone and studied the associations to patient-reported International Prostate Symptom Score (IPSS) [10]. Palorini et al. analysed the acute symptoms using dose-surface maps [6]. The studies, however, either reduced the comparisons to a single point, probably to avoid multiple-comparison problems [9], re-contoured an especially difficult structure [10], analysed a small number of patients [6] and/or were limited to generalised or acute urinary symptoms [6, 10]. Further confirmation in independent cohorts is needed to assess the repeatability of the observations and whether the impact of dose to specific subregions is observable for specific symptoms like dysuria, incontinence and haematuria.

To assess the association of the spatial dose distribution to the bladder to the formation of urinary symptoms, this work adapted the methods used to develop dose-surface maps of the rectum through organ unfolding to produce maps visualising the dose received by the bladder surface. From the developed maps, pixel-wise analyses were performed. Data from patients accrued to the Trans-Tasman Radiation Oncology Group (TROG) 03.04 trial of Randomised Androgen Deprivation and Radiotherapy (RADAR-NCT00193856) were utilised [11, 12].

MATERIALS AND METHODS

Patients and treatments

The RADAR trial examined the influence of the duration of androgen deprivation with or without bisphosphonate treatment, adjuvant with radiotherapy [11, 12]. Patients were accrued from 2003 to 2008 in 23 centres across Australia and New Zealand. Extensive and centralised technical quality assurance (QA) was utilised, which included a combination of manual and automatic review of each patient's treatment plan against protocol requirements [13, 14]. Data collection, protocol requirements, treatment technique and QA have been summarised previously [11-13, 15, 16]. 754 participants received 3-dimensional conformal external beam radiotherapy (EBRT) (without a brachytherapy boost) to either 66, 70 or 74 Gy and had complete bladder dose data collected, comprising a digital treatment plan export including axial computed tomography (CT) images and associated planned dose matrix. The patient was treated either prone or supine according to departmental preference. Bladder filling strategy was consistent between planning CT and throughout the treatment.

Symptom measurement and definition

Following treatment, patients were routinely followed up every three months for 18 months, then six-monthly up to five years and then annually. Atomised symptoms (dysuria, haematuria and incontinence) were considered using grades from the physician-assessed LENT-SOMA [17] (Supplementary material A) and the IPSS. For each symptom, one definition was chosen based on the clinical relevance, availability of acceptable number of events for model stability and the optimal definition to find dose-symptoms relationship as discussed in previous histogram-based analysis [7]. The endpoints were: dysuria grade ≥ 2 , haematuria grade ≥ 1 and the count of incontinence grade ≥ 2 events. Urinary frequency had been shown to be associated to the mean dose received by the bladder and the spatial dose information is not expected to provide additional information and was therefore not considered [7]. For overall urinary symptoms, the IPSS was utilised with patients with ≥ 10 points increase from the baseline were considered having symptoms ($\Delta\text{IPSS} \geq 10$). Patients with baseline IPSS > 20 were excluded. Focusing on the late effect, follow-ups at least one year after randomisation (i.e. five months after the end of EBRT) were considered. Follow-up data were frozen at November 2012.

Bladder dose-surface maps construction

The digital RT treatment plan for every patient was independently reviewed and archived [14, 16]. To visualise the spatial dose distribution, the bladder surface was virtually unfolded by cutting through the anterior of the bladder and mapping the dose and location information onto a 2-dimensional surface using an in-house developed routine. The slice thicknesses of the bladder region of the original CT scans varied from approximately 1 mm to 5 mm, sometimes within the same patient. Consequently, the CTs were resampled to a standard 1 mm slice thickness. The dose values for selected points on the bladder were then interpolated from the dose grids. The sagittal slice cutting through the bladder centre-of-mass was used as a guide to determine the most anterior and most posterior point for each 1 mm slice of the bladder. The surface was aligned to the posterior point on the y-axis and the most inferior point (bladder base) to the x-y intersection. The anterior-posterior-anterior dose and location information was then normalised onto 201 pixels (100 pixels each to the right and left of the posterior point) on the x-axis and the inferior-superior dose and location information for the first 45 mm of bladder length onto 45 pixels on the y-axis. For 158 patients with an inferior-

superior bladder length < 45 mm, the data points beyond their actual bladder length were considered missing. Physical doses from 1.8 to 2.2 Gy per fraction were converted to EQD2 (equivalent dose in 2 Gy fractions) using $\alpha/\beta=6$ Gy [18]. The approximate location of trigone area in the posterior-inferior region was represented by a point at 15 mm above the base.

Pixel-wise comparisons

Pixel-wise comparisons between the maps for patients with and without symptoms were performed using a standardised Wilcoxon rank sum test. For incontinence, the comparisons were performed between patients with no or one event to patients with ≥ 2 events of grade ≥ 2 incontinence. Raw p -values were reported alongside the step-down maxT permutation-based adjusted p -values described in Westfall & Young [19], a commonly utilised method in genomics [20]. The method takes into account the dependence structure among test statistics, suitable for highly correlated variables like the dose maps [20]. For interested readers, a review by Dudoit et al. is recommended [20]. As there are many methods for multiple comparisons adjustments in the literature, differing in complexity and conservatism, reporting the adjusted p -values alone may potentially confound readers unfamiliar with issues related to multiple comparisons adjustment. Additionally, multiple comparisons adjustments are also prone to abuse in image-based comparisons. For example, researchers may arbitrarily reduce/increase the resolution of dose maps to synthetically reduce/increase the number of comparisons resulting in markedly different outcomes of multiple comparisons adjustment. This may complicate the pooling of knowledge from different studies. Reporting one relatively conservative adjustment alongside unadjusted comparisons would allow readers to make a more informed conclusion by also looking at the pattern of associations rather than focusing on specific highly-significant pixels.

Adjustments for clinical factors

For each pixel in the dose-surface maps, the relationship between the dose and dysuria, haematuria and Δ IPSS10 was calculated using a logistic regression model. For incontinence, the relationship was assessed by means of an event-count model to take into consideration the multiple events using negative binomial regression [7, 21]. Due to the known impact of clinical factors and to obtain the least-biased estimate of the effect of dose on the development of symptoms, adjustments were performed for clinical factors including baseline symptom and trial arm, which have previously been found to impact symptom development (details provided in Supplementary Material B and [22-24]). To adjust for underestimation for patients accrued at later dates, the number of available follow-ups was included as a covariate. The pattern of relationship between each pixel in the maps and symptoms is discussed in terms of the distribution of p -values of the dose features. p -Values < 0.05 were considered significant and p -values < 0.20 to indicate suggestive association. The models were constructed as implemented in MASS (version 7.3-40) in R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) [25].

RESULTS

The median length of late follow-up time was 72 months (range: 58-108). Grade ≥ 2 dysuria was observed in 59 patients, 101 patients had grade ≥ 1 haematuria, 91 had at least a single event of grade ≥ 2 incontinence and 36 had at least two events of grade ≥ 2 incontinence from which 21, 8, 3, 2 and 2 patients had 2, 3, 4, 5 and 6 events, respectively. 94 of 711 patients with baseline score of ≤ 20 had Δ IPSS10.

The average dose map (Fig. 1A) shows the dose to be highest in the posterior-inferior region, closest to the planning target volume, reducing further anterior and being lowest in the anterior-superior region. The highest standard deviations were in the posterior-superior region (>24 Gy) and lowest in the anterior-superior and posterior-inferior regions (<8 Gy) (Fig. 1B). At the level of 15 mm from the base (the approximate location of the trigone), the dose across all patients was negatively correlated to dose at the most anterior point at the same level (Spearman rho, $\rho = -0.25$) potentially due to increasing field conformity for patients treated to higher prescription dose as described in [22] and moderately correlated to dose at most lateral left ($\rho = 0.49$) and right ($\rho = 0.45$) points (Supplementary material C).

The associations of the spatial dose measures to urinary symptoms were found to be dependent on specific symptoms (Fig. 2). The p -values for dose comparisons with and without adjustment for clinical factors show a similar pattern (Fig. 2 I-P). In the comparison using standardised Wilcoxon rank sum test, the adjusted p -values were significant for dysuria at the anterior-inferior and incontinence at the lateral-inferior area (Fig. 2 I&K). The doses located at the anterior-inferior of the bladder were found to have the strongest relationship to dysuria (Fig. 2 I&M). The area at the most posterior points resulted in no associations ($p > 0.2$). The associations to dysuria was highly significant at points in the anterior to lateral region (min: $p = 0.0002$, adjusted: 0.041) while the most posterior region at the estimated trigone level (15 mm) was found to have no association ($p = 0.835$). The area highly associated to dysuria did not coincide with the area with the highest dose variance (posterior-superior (>24 Gy) and did not have a markedly different standard deviation to the most posterior region where the trigone location is estimated (both have standard deviations between 14-16 Gy). The area found to be associated to haematuria was located at anterior-inferior and posterior-superior regions (Fig.2 J&N). The dose at the most inferior region, especially close to the left and right lateral points of the bladder, was found to be significantly associated to incontinence (Fig.3 K&O). For Δ IPSS10, the dose to the area at 15-20 mm from base at the anterior of the bladder showed positive associations while the dose at the posterior-inferior region showed negative associations (Fig.3 L&P).

DISCUSSION

The spatial information afforded by the dose-surface maps presented here, in combination with the utilisation of both atomised and generalised symptoms, provide a strong foundation for understanding the impact of regional dose distribution on the development of symptoms of urinary dysfunction. A spatially-variable association between the bladder surface dose and symptoms was found, with dysuria, haematuria and generalised urinary symptoms primarily associated with dose to the anterior-inferior and posterior-superior bladder surface, and incontinence to the dose to the lateral-inferior bladder surface. This study adds to the few studies on spatial dose distribution impacts on urinary symptoms.

The importance of the dose to bladder trigone and bladder neck to urinary dysfunction was identified in previous studies [6, 9, 10, 26]. In the current study, including atomised symptoms and Δ IPSS10, it was found that the dose to the posterior-inferior of the bladder, coinciding with the bladder trigone, only showed a similar association for urinary

incontinence. The associations are likely related to the dose received by the preprostatic sphincter, comprised of smooth muscle fibres responsible for aiding urinary continence or detrusor overactivity [27, 28]. The higher doses laterally at this level may add to the ischemia and fibrosis of the bladder neck and hence incontinence. As dose to the region is closely associated to the prescribed dose, it is expected that dose escalation may increase the incidence of urinary incontinence. However, a large-scale dose escalation study found otherwise [29].

The exact location of the trigone area is inherently difficult to visualise in CT images with the urethra and bladder ureteral openings only visible in a portion of patients. This could explain why only an approximate location was derived in a previous study [9]. Ghadjar et al., however, had successfully delineated the trigone area of all 268 patients [10]. In the current study, due to the resources required to reliably delineate the trigone area of 754 patients, dose-surface maps production was automated instead and trigone dose was estimated by that to the inferior-posterior portion of the dose-surface maps. Dose-surface maps are advantageous as they provide the overall distribution of the bladder rather than dose to just a point or a specific bladder sub-region. It is probably a more reasonable method to assess the impact of dose to a sub-region like bladder trigone because, first, the process to delineate these regions, similar to other anatomical features with low visibility on CT images, may be prone to errors. Second, until magnetic resonance imaging (MRI)-based planning is made widely available, delineation of the trigone area is not likely to be a standard in the clinical setting.

Despite finding more pronounced associations with obstruction incidence of the area cranial to the trigone area than the trigone itself, Heemsbergen et al. concluded the importance of the dose to the trigone area to predict urinary obstruction [9]. It was speculated that, among other effects, such associations were the result of larger dose variance at the region compared to that at the trigone and the strong correlation in dose between the two points. The same conclusion cannot be reached in the current study. The regions with strongest association did not have a markedly different standard deviation to the most posterior region where the trigone is located. For Δ IPSS10, the negative associations to the posterior-inferior region were in contrast to what was observed by Ghadjar et al. [10]. Also, the dose at the most posterior point at 15 mm from base was only moderately correlated to the most anterior dose at the same level. These observations strengthened the conclusion that dysuria, haematuria and Δ IPSS10 were not associated to the dose received by the bladder trigone. Thus, the observations require alternative explanations to the one previously suggested [9, 10]:

1. The importance of the dose to the anterior and superior regions is potentially only a surrogate of the high dose area encapsulating the bladder, previously found to be predictive in dose-surface histogram analyses [7]. This theory of volume effect matches with the known pathophysiological origin of radiation-induced haematuria which is likely due to a direct assault on the integrity of epithelial cell lining from radiation proportional to the area of tissue receiving a certain high dose. Presumably with a bigger volume of bladder urothelium affected there is an increased risk of ulceration/chronic inflammation. The circumferential high-dose region was predictive of acute symptoms in another study suggesting the volume effects [6]. This explanation may discount the need for dose maps because the area

receiving a certain high dose is well-described using simpler dose-surface histograms.

2. The high dose to the anterior and superior extent temper the coordination of normal micturition function. Normal micturition is a complex process requiring the activation of the micturition reflex from the detection of bladder filling by the stretch receptors and the excitation of the detrusor muscle by efferent signals which may be at risk of attritions [30]. Direct injury from the irradiation of the bladder wall can impact the elastic properties of the wall which may inhibit contraction of the voiding detrusor muscle, consequently increasing the risk of urinary retention [30, 31].
3. The dose to the anterior and superior regions may also correlate to dose to other organs in the genitourinary system outside bladder. Further works are anticipated to properly investigate this possibility including the dose to the posterior prostatic urethra and the anterior urethra including membranous and bulbous urethra.
4. The region with high significance may be related to areas with the lowest intrafractional movement (i.e. the base) [32].

The patients analysed here were treated with no standard dose constraints applied to the bladder probably owing to the historical observations that there is no clear dose-volume relationship for the bladder in the dose range used in clinical treatments [18]. Only recently has the impact of dose distributions to the bladder been extensively studied suggesting a significant impact of dose distribution potentially superseding the previous hypotheses [7, 9, 10, 23]. In this analysis, it was found that the dose received by the anterior of the bladder was predictive, thus, clinically, this can provide motivation to limit the high dose extending anteriorly. The current study was based on planning images providing only a surrogate of the actual dose received [33]. We are waiting for results from cohorts where repeated anatomical imaging has been undertaken throughout treatment fractions, allowing deformable registration of the bladder surface at each fraction, to augment the observations above.

In conclusion, a spatially-variable response of the bladder surface was found following external beam radiotherapy of the prostate. The bladder trigone area is only likely to be an area of interest for incontinence. The observation from this study suggests the need for spatially-based bladder dose constraints especially the dose extending anteriorly.

ACKNOWLEDGEMENTS

We acknowledge funding from Cancer Australia and the Diagnostics and Technology Branch of the Australian Government Department of Health and Ageing (grant 501106), the National Health and Medical Research Council (grants 300705, 455521, 1006447), the Hunter Medical Research Institute, the Health Research Council (New Zealand), the University of Newcastle and the Calvary Mater Newcastle, Abbott Laboratories, Novartis Pharmaceuticals. We gratefully acknowledge the support of the participating RADAR centres and the Trans-Tasman Radiation Oncology Group. We are grateful to Michelle Krawiec and Sharon Richardson for delineating bladder structures on trial datasets, Stefano Gianolini for providing inputs on dose-maps development, and Claudio Fiorino, Frederica Palorini and Tiziana Rancati for helpful comments.

Reference

- [1] Buettner F, Gulliford SL, Webb S, Partridge M. Using dose-surface maps to predict radiation-induced rectal bleeding: a neural network approach. *Phys Med Biol*. 2009;54:5139-53.
- [2] Acosta O, Drean G, Ospina JD, et al. Voxel-based population analysis for correlating local dose and rectal toxicity in prostate cancer radiotherapy. *Phys Med Biol*. 2013;58:2581-95.
- [3] Munbodh R, Jackson A, Bauer J, Schmidlein CR, Zelefsky MJ. Dosimetric and anatomic indicators of late rectal toxicity after high-dose intensity modulated radiation therapy for prostate cancer. *Med Phys*. 2008;35:2137-50.
- [4] Lee R, Chan EK, Kosztyla R, Liu M, Moiseenko V. Dose-distance metric that predicts late rectal bleeding in patients receiving radical prostate external-beam radiotherapy. *Phys Med Biol*. 2012;57:8297-307.
- [5] Wortel RC, Witte MG, van der Heide UA, et al. Dose-surface maps identifying local dose-effects for acute gastrointestinal toxicity after radiotherapy for prostate cancer. *Radiother Oncol*. 2015;117:515-20.
- [6] Palorini F, Cozzarini C, Gianolini S, et al. First application of a pixel-wise analysis on bladder dose-surface maps in prostate cancer radiotherapy. *Radiother Oncol*. 2016;119:123-8.
- [7] Yahya N, Ebert MA, Bulsara M, et al. Urinary symptoms following external beam radiotherapy of the prostate: Dose-symptom correlates with multiple-event and event-count models. *Radiother Oncol*. 2015;117:277-82.
- [8] Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31:1257-80.
- [9] Heemsbergen WD, Al-Mamgani A, Witte MG, van Herk M, Pos FJ, Lebesque JV. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics. *Int J Radiat Oncol Biol Phys*. 2010;78:19-25.
- [10] Ghadjar P, Zelefsky MJ, Spratt DE, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;88:339-44.
- [11] Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial. *Lancet Oncol*. 2014;15:1076-89.
- [12] Denham JW, Steigler A, Joseph D, et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. *Radiother Oncol*. 2015;115:301-7.
- [13] Ebert MA, Bulsara M, Haworth A, et al. Technical quality assurance during the TROG 03.04 RADAR prostate radiotherapy trial: are the results reflected in observed toxicity rates? *J Med Imaging Radiat Oncol*. 2015;59:99-108.
- [14] Ebert MA, Haworth A, Kearvell R, et al. Detailed review and analysis of complex radiotherapy clinical trial planning data: evaluation and initial experience with the SWAN software system. *Radiother Oncol*. 2008;86:200-10.

- [15] Haworth A, Kearvell R, Greer PB, et al. Assuring high quality treatment delivery in clinical trials - Results from the Trans-Tasman Radiation Oncology Group (TROG) study 03.04 "RADAR" set-up accuracy study. *Radiother Oncol.* 2009;90:299-306.
- [16] Kearvell R, Haworth A, Ebert MA, et al. Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 'RADAR' trial. *J Med Imag Radiat On.* 2013;57:247-57.
- [17] Lent soma scales for all anatomic sites. *Int J Radiat Oncol Biol Phys.* 1995;31:1049-91.
- [18] Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys.* 2010;76:S116-22.
- [19] Westfall PH, Young SS. Resampling-based multiple testing : examples and methods for P-value adjustment. New York: Wiley; 1993.
- [20] Dudoit S, Shaffer JP, Boldrick JC. Multiple hypothesis testing in microarray experiments. *Stat Sci.* 2003;18:71-103.
- [21] Cox S, West SG, Aiken LS. The analysis of count data: a gentle introduction to poisson regression and its alternatives. *J Pers Assess.* 2009;91:121-36.
- [22] Denham JW, Wilcox C, Lamb DS, et al. Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. *Radiother Oncol.* 2012;105:184-92.
- [23] Yahya N, Ebert MA, Bulsara M, et al. Dosimetry, clinical factors and medication intake influencing urinary symptoms after prostate radiotherapy: An analysis of data from the RADAR prostate radiotherapy trial. *Radiother Oncol.* 2015;116:112-8.
- [24] Denham JW, Wilcox C, Joseph D, et al. Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. *Lancet Oncology.* 2012;13:1260-70.
- [25] R Development Core Team. R: a language and environment for statistical computing. 2013. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0; 2013.
- [26] Hathout L, Folkert MR, Kollmeier MA, Yamada Y, Cohen GN, Zelefsky MJ. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for treatment planning. *Int J Radiat Oncol Biol Phys.* 2014;90:312-9.
- [27] McLaughlin PW, Troyer S, Berri S, et al. Functional anatomy of the prostate: implications for treatment planning. *Int J Radiat Oncol Biol Phys.* 2005;63:479-91.
- [28] Thiruchelvam N, Cruz F, Kirby M, Tubaro A, Chapple CR, Sievert KD. A review of detrusor overactivity and the overactive bladder after radical prostate cancer treatment. *BJU Int.* 2015;116:853-61.
- [29] Al-Mamgani A, van Putten WL, Heemsbergen WD, 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.
- [30] Drake MJ, Williams J, Bijos DA. Voiding dysfunction due to detrusor underactivity: an overview. *Nat Rev Urol.* 2014;11:454-64.
- [31] Choo R, Do V, Herschorn S, et al. Urodynamic changes at 18 months post-therapy in patients treated with external beam radiotherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys.* 2002;53:290-6.
- [32] Pinkawa M, Asadpour B, Siluschek J, et al. Bladder extension variability during pelvic external beam radiotherapy with a full or empty bladder. *Radiother Oncol.* 2007;83:163-7.

[33] Andersen ES, Muren LP, Sorensen TS, et al. Bladder dose accumulation based on a biomechanical deformable image registration algorithm in volumetric modulated arc therapy for prostate cancer. *Phys Med Biol.* 2012;57:7089-100.

Legends:

Figure 1: The mean (left) and standard deviation (right) dose maps in Gy for all patients. *Abbreviations:* A=anterior; P=posterior, R=right, L=left.

Figure 2: Visualisation of the results on maps. Row 1: median dose maps for patients with symptoms below thresholds; row 2: median maps for patients with symptoms at and above threshold; row 3: dose difference maps (black lines represent area with Wilcoxon signed-rank unadjusted $p < 0.05$, pink lines represent area with adjusted $p < 0.05$), only positive difference shown; row 4: area of significance after adjustments for clinical factors using multivariate logistic regression or event-count model with the mean dose map on the background for dysuria (A, E, I, M), haematuria (B, F, J, N), incontinence (C, G, K, O) and International Prostate Symptom Score (IPSS) increase of ≥ 10 (D, H, L, P). Thresholds: dysuria=grade 2, haematuria=grade 1, incontinence=two or more events of grade ≥ 2 . The gridded area in P represents area with negative coefficients (i.e. higher dose produced lower risk).

Figure 1: The mean (left) and standard deviation (right) dose maps in Gy for all patients.
Abbreviations: A=anterior; P=posterior, R=right, L=left.

Figure 2: Visualisation of the results on maps. Row 1: median dose maps for patients with symptoms below thresholds; row 2: median maps for patients with symptoms at and above threshold; row 3: dose difference maps (black lines represent area with Wilcoxon signed-rank unadjusted $p < 0.05$, pink lines represent area with adjusted $p < 0.05$), only positive difference shown; row 4: area of significance after adjustments for clinical factors using multivariate logistic regression or event-count model with the mean dose map on the background; row 5: the odds ratio for 10 Gy increase of the dose for dysuria (A, E, I, M, Q), haematuria (B, F, J, N, R), incontinence (C, G, K, O, S) and International Prostate Symptom Score (IPSS) increase of ≥ 10 (D, H, L, P, T). Thresholds: dysuria=grade 2, haematuria=grade 1, incontinence=two or more events of grade ≥ 2 . The gridded area in P represents area with negative coefficients (i.e. higher dose produced lower risk).

Supplementary material A: The LENT-SOMA grading system

	Grade 0	Grade 1	Grade 2	Grade 3
Dysuria	Occasional and mild	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Haematuria	None	Microscopic, normal haemoglobin	Intermittent macroscopic, <10% decrease in haemoglobin	Persistent macroscopic, 10-20% decrease in haemoglobin.
Incontinence	None	With coughing and sneezing	Spontaneous, some control	No control

Supplementary material XX: Distributions of investigated variables. Continuous distributions are specified as mean $\pm$ standard deviation (range), categorical variables are specified as number of patients (%). The inclusion of the clinical factors in the pixel-wise analysis was based on univariate analysis of the factors. For a more complete report of the clinical factors, refer [23].

Factors		Dysuria		Haematuria		Incontinence		ΔIPSS10	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Physical & Trial factors									
Age	69 ± 7(49-85) years	NS	NS	NS	NS	NS	NS	NS	NS
BMI	27.98 ± 4.12 (17.17-45.77) kg/m ²	NS	NS	NS	NS	NS	NS	NS	NS
ECOG Performance Status (=1)	123 (16%)	NS	NS	NS	NS	NS	NS	NS	NS
Arm	A (191);	NS	NS	NS	NS	NS	NS	1	-
	B (187),							0.93 (0.44 – 1.95)	0.841
	C (192),							1.48 (0.76 – 2.87)	0.246
	D (184) (refer to [22, 24])							1.91 (1.00-3.64)	0.049
Comorbidities									
Cardiovascular condition	217 (29)	NS	NS	NS	NS	NS	NS	NS	NS
Peripheral vascular condition	44 (6)	NS	NS	NS	NS	NS	NS	NS	NS
Cerebrovascular condition	37 (5)	NS	NS	NS	NS	3.79 (1.51 – 9.52)	0.005	NS	NS
Hypertension	353 (49)	NS	NS	NS	NS	NS	NS	NS	NS
Dyslipidaemia	248 (33)	1.86 (1.03 – 3.36)	0.040	NS	NS	NS	NS	NS	NS
NIDDM	92 (12)	NS	NS	NS	NS	NS	NS	NS	NS
Respiratory disorder	99 (13)	NS	NS	NS	NS	NS	NS	1.89 (1.05 – 3.41)	0.035
Bowel disorder	91 (12)	3.14 (1.58 – 6.23)	0.001	3.58 (1.21 – 10.57)	NS	NS	NS	NS	NS
Dermatological disorder	52 (7)	NS	NS	NS	NS	NS	NS	NS	NS
Bone or calcium metabolism disorder	66 (9)	NS	NS	NS	NS	NS	NS	NS	NS

Haematological disorder	11 (1)	NS	NS	NS	NS	NS	NS	NS	NS
Thyroid disorder	24 (3)	NS	NS	NS	NS	NS	NS	NS	NS
Baseline dysuria	Grade 0 – 660 (88.2)	1.86 (1.11-3.12) / grade	0.018	-	-	-	-	-	-
	Grade 1 – 71 (9.5)								
	Grade 2 – 15 (2.0)								
	Grade 3 – 2 (0.3)								
Baseline haematuria	Grade 0 – 729 (97.5)	-	-	NS	NS	-	-	-	-
	Grade 1 – 19 (2.5)								
Baseline incontinence	Grade 1 – 718 (96.0)	-	-	-	-	3.01 (1.34 – 6.75)	0.008	-	-
	Grade 2 – 25 (3.3)								
	Grade 3 – 5 (0.7)								
Baseline IPSS score	1 - 23 (3.66)	-	-	-	-	-	-	0.95 (0.90-1.00)	0.049
	2 – 63 (10.03)								
	3 – 69 (10.99)								
	4 – 56 (8.92)								
	5 – 59 (9.39)								
	6 – 37 (5.89)								
	7 – 52 (8.28)								
	8 – 51 (8.12)								
	9 – 25 (3.98)								
	10 – 35 (5.57)								
	11 – 32 (5.10)								
	12 – 20 (3.18)								
	13 – 21 (3.34)								
	14 – 11 (1.75)								
	15 – 17 (2.71)								
	16 – 18 (2.87)								
	17 – 8 (1.27)								
	18 – 9 (1.43)								
	19 – 14 (2.23)								
	20 – 8 (1.27)								
Medication intake									
Hypoglycaemic agents	55 (7)	NS	NS	NS	NS	NS	NS	NS	NS
ACE Inhibitor	240 (32.1)	NS	NS	NS	NS	NS	NS	NS	NS
Statin	221 (29.6)	NS	NS	NS	NS	NS	NS	NS	NS
NSAID	136 (18.2)	NS	NS	NS	NS	NS	NS	NS	NS

Anti-coagulant	120 (16.0)	NS	NS	NS	NS	NS	NS	NS	NS
Lifestyle factors									
Smoking status	Never 274 (36); Previous 380 (50);	1 1.61 (0.79 – 3.28)	- 0.19	NS	NS	NS	NS	NS	NS
	Current 99 (13)	3.36 (1.45 – 7.80)	0.005						
Alcohol intake	None 100 (13); Occasional 279 (37);	NS	NS	NS	NS	NS	NS	1 0.46 (0.24- 0.88)	- 0.019
	Regular 370 (49)							0.53 (0.29- 0.97)	0.039

Abbreviations; OR- Odds ratio; BMI - body mass index; ECOG - ECOG Performance Status; NIDDM – non-insulin dependent diabetes mellitus; IDDM – insulin dependent diabetes mellitus; ACE - angiotensin-converting-enzyme; NSAID – non-steroidal anti-inflammatory drugs; NS- not significant.

Supplementary material C: Spearman correlation matrix for the dose-maps represented by the posterior-most (P), anterior-most (A), left (L) and right (R) pixels in every 5mm increment from base.