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Original Research Article

Developing and validating a simple urethra surrogate model to facilitate dosimetric analysis to predict genitourinary toxicity

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ABSTRACT

Purpose: The urethra is a critical structure in prostate radiotherapy planning; however, it is impossible to visualise on CT. We developed a surrogate urethra model (SUM) for CT-only planning workflow and tested its geometric and dosimetric performance against the MRI-delineated urethra (MDU).

Methods: The SUM was compared against 34 different MDUs (within the treatment PTV) in patients treated with 36.25Gy (PTV)/40Gy (CTV) in 5 fractions as part of the PACE-B trial. To assess the surrogate's geometric performance, the Dice similarity coefficient (DSC), Hausdorff distance (HD), mean distance to agreement (MDTA) and the percentage of MDU outside the surrogate (UOS) were calculated. To evaluate the dosimetric performance, a paired *t*-test was used to calculate the mean of differences between the MDU and SUM for the D99, D98, D50, D2 and D1. The D(n) is the dose (Gy) to n% of the urethra.

Results: The median results showed low agreement on DSC (0.32; IQR 0.21–0.41), but low distance to agreement, as would be expected for a small structure (HD 8.4mm (IQR 7.1–10.1mm), MDTA 2.4mm (IQR, 2.2mm-3.2mm)). The UOS was 30% (IQR, 18–54%), indicating nearly a third of the urethra lay outside of the surrogate. However, when comparing urethral dose between the MDU and SUM, the mean of differences for D99, D98 and D95 were 0.12Gy (p=0.57), 0.09Gy (p=0.61), and 0.11Gy (p=0.46) respectively. The mean of differences between the D50, D2 and D1 were 0.08Gy (p=0.04), 0.09Gy (p=0.02) and 0.1Gy (p=0.01) respectively, indicating good dosimetric agreement between MDU and SUM.

Conclusion: While there were geometric differences between the MDU and SUM, there was no clinically significant difference between urethral dose-volume parameters. This surrogate model could be validated in a larger cohort and then used to estimate the urethral dose on CT planning scans in those without an MRI planning scan or urinary catheter.

1. Introduction

Prostate radiotherapy is a key radical treatment for localised prostate cancer [1]. The treatment techniques continue to evolve due to technological advancements, improved image guidance, and a better understanding of prostate cancer's radiobiology [2–4]. We can now deliver more precise and ablative doses using external beam radiotherapy techniques such as stereotactic body radiotherapy (SBRT), and focal boost approaches [2,3,5,6]. However, urinary toxicity remains a major concern for both clinicians and patients. The phase III international randomised PACE-B trial demonstrated higher grade 2+ urinary side-effects at 2 years with SBRT (12%) compared with conventionally fractionated radiotherapy (6%), when measured using the Common Terminology Criteria for Adverse Events (CTCAE) [7]. It is postulated that genitourinary toxicity endpoints have a low alpha/beta ratio (0.6 to 2.0Gy), and therefore the therapeutic gain from extreme

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hypofractionation may be lower than anticipated [8]. As the prostatic urethra traverses the clinical target volume, it is bound to receive the prescription dose or higher, and subsequent radiation-induced injury could lead to stricturing or symptoms such as dysuria, nocturia, urgency, haematuria, and incontinence [9–11].

The correlation between intraprostatic urethral dose and late toxicity is well-established following brachytherapy. It has recently been shown that similar correlations could exist following prostate SBRT [11–14]. There is also increasing evidence that urethra-sparing radiotherapy can reduce urinary toxicity without compromising tumour control [15]. However, we still lack validated and robust urethral dose constraints for 'urethral steering' radiotherapy (limiting hotspots to the urethra) to mitigate late urinary toxicity. To develop these constraints, it is necessary to delineate the intraprostatic urethra and to perform comprehensive dose-volume toxicity modelling. Unfortunately, urethral segmentation on CT planning scans is impossible due to lower soft tissue contrast resolution compared with MRI.

One method of identifying the urethra involves the insertion of a Foley catheter. This, however, is uncomfortable for patients, requires trained personnel for insertion, risks introducing infection, and can shift the urethral position [16,17]. Another method includes delineating the urethra on MRI planning scans, which often appears moderately hyperintense on T2-weighted imaging [18]. However, most large clinical trials with robust toxicity datasets have a CT-only-based workflow, and do not stipulate urinary catheter insertion at CT planning.

Several studies have proposed techniques for identifying the urethra in a CT-only-based workflow, mainly in the setting of prostate brachytherapy. Earlier approaches include using the geometric centre of the prostate, or a deviated surrogate [19,20]. This has evolved to a multi-atlas-based segmentation method, and now recently to deep-learning urethra segmentation models [21–24]. However, most approaches have been trained and tested against the urethra identified by a urinary catheter, which can shift the original urethral position [16,17]. In this paper, we propose a simple surrogate urethra model, developed using MRI-delineated urethras, for those with a CT-only-based workflow. We validated this surrogate model by comparing its geometric performance against MRI-delineated urethras and evaluating differences in urethra dose-volume parameters. We aim to utilise this surrogate model in future work to retrospectively delineate the urethra in CT planning scans to facilitate dose-volume toxicity modelling.

2. Methods

The surrogate urethra was developed using radiotherapy planning MRI scans of patients treated in the PACE-C trial at The Royal Marsden Hospital, UK. The study is a randomised control trial testing the use of prostate SBRT in intermediate/high risk prostate cancer. All patients had a CT planning scan of 1.5mm slice thickness, and the urethra was contoured on 2.5mm thickness T2-weighted planning MRI. The planning MRI scans were performed in the treatment position. The CT and MRI scans were fused using implanted gold seed fiducial markers, and urethras were contoured by treating clinicians on the fused images. The prostate and proximal 1cm of seminal vesicle (CTVpsv) received 40Gy in 5Fr, with the dose to 95% of the CTVpsv (D95%) aimed to at least 40Gy. The CTVpsv was expanded 5mm isotropically, except for posteriorly in which the margin was 3–5mm. The PTVpsv received 36.25Gy in 5Fr, with the PTVpsv D95% at least 36.25Gy. The prostate and proximal 2cm of seminal vesicle (CTVsv) was expanded 5mm isotropically, and the PTVsv received 30Gy in 5Fr, with the PTVsv D95% at least 30Gy. Dose heterogeneity within the target was acceptable, such that a maximum dose greater than 45Gy was allowed.

2.1. Development of the surrogate urethra model

Initially, 41 MRI-delineated urethras (MDU) were reviewed with a consultant uroradiologist (SJW, with 6 years' experience in prostate MRI, considered expert having reported >2000 studies**)** to ensure accurate urethral delineation [25]. Contours were deemed unacceptable if greater than 50% of the MDU volume were outside the 'true' urethra in two or more slices. Two cases were excluded due to the presence of a transurethral resection of the prostate (TURP) defect, leaving a total of 39 cases for developing the surrogate model. The median prostate volume for the 39 'training' cohort was 38.4cm^3 (range, 15.4–76.3cm^3). An in-house Python script integrated into the RayStation (Raysearch Laboratories, Stockholm) treatment planning system was employed to extract the urethral diameter, prostate diameter, and position of the urethra on the mid-sagittal slice (also known as relative urethra position (RUP)) for each 1.5mm CT slice. The RUP is calculated by measuring distance between the centre of the urethra and posterior wall of the prostate, divided by the anterior-posterior prostate diameter in the mid-sagittal slice. Fig. 1 highlights how the RUP is calculated in the axial plane. A RUP of >0.5 means the urethra is closer to the anterior edge of the prostate than the posterior edge at that level.

The average position of the urethra on the mid-sagittal slice i.e. RUP was calculated at four specific locations along the prostate (3/4 gland, mid-gland, 1/4 gland and apex). The average RUP at the 3/4 gland, mid-gland, 1/4 gland and apex for the 39 cases were 0.51, 0.39, 0.43 and 0.72, respectively. The corresponding positions were entered into a Python script, which places a 10mm diameter circle at these positions on the centre of the x-axis. The script creates additional interpolated 10mm diameter circles, in between the circles in the 3/4 gland, mid-gland, 1/4 gland and apex (Fig. 2). A 10mm diameter surrogate was selected because of its superior performance in terms of the percentage of urethra outside the surrogate (UOS) compared to a 6mm diameter surrogate (Appendix Table 1). On average, the most inferior slice for the 39 MDU was found to be 3mm inferior and 3mm anterior to the most apical slice of the prostatic urethra. Due to significant anatomical variations at the bladder/prostate interface e.g., presence of a median lobe, the observer placed a 10mm diameter circle at the estimated urethra position at the prostate base. In some cases, the urethra opening could be visualised on CT imaging (Fig. 3), while in others, it was inferred by reviewing the sagittal reformatted images. Fig. 4 provides a summary of the methodology used to develop and validate the surrogate model.

2.2. Evaluating geometric performance of surrogate urethra

The accuracy of the surrogate urethra was assessed in a different cohort of MRI-delineated urethras, not used in the initial surrogate development. Using patients from the PACE-B study recruited at Royal Marsden Hospital, 34 MDU (within the treatment planning target volume) were compared with the surrogate urethra. The median prostate volume in the 34 'testing' cohort was 54.4cm^3 (range, 30.0–162.8cm^3).

The geometric performance of the surrogate model was assessed using the dice similarity coefficient (DSC), which measures the spatial overlap between two segmentations. A DSC of 0 indicates no overlap, while a DSC of 1 represents complete overlap [26]. The mean distance to agreement (MDTA) was calculated using a distance transformed base approach. In this method, each point on the surface of the surrogate is assigned a minimum distance to the closest point on the surface of the MDU. Similarly, each point on the surface of the MDU is assigned a minimum distance to the closest point on the surface of the surrogate. The MDTA represents the average of these distances measured in millimetres. A lower MDTA indicates a better concordance between the two structures [27]. The Hausdorff distance utilises a similar approach to the MDTA. However, instead of calculating the average distance, it considers the maximum distance between corresponding points on the SUM and MDU surface [28]. This provides a measure of the maximum separation between the two structures. The percentage of the MDU outside the surrogate (UOS) is a metric that quantifies the volume of the MDU that lies outside the surrogate urethra. A UOS of 0% indicates complete overlap between the MDU and the surrogate model.

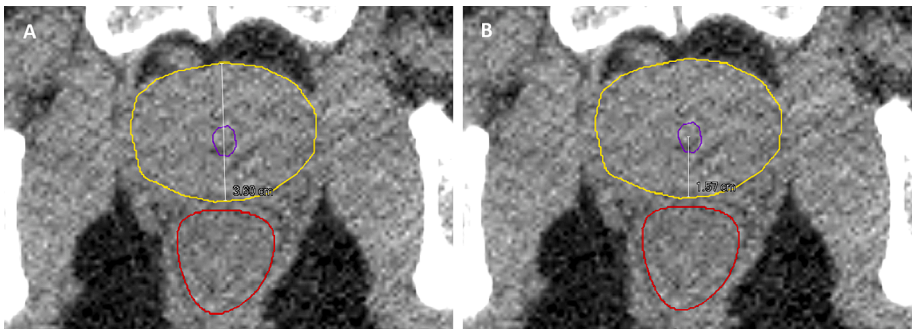

Fig. 1. CT planning scan demonstrating relative urethra position (RUP) calculation. The anterior-posterior prostate diameter is measured at 3.60cm (A). The distance of the central urethra from the posterior wall is measured at 1.57cm (B). The relative urethra position (RUP) = 0.44. Urethra (purple), prostate and proximal seminal vesicle (yellow) and rectum (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

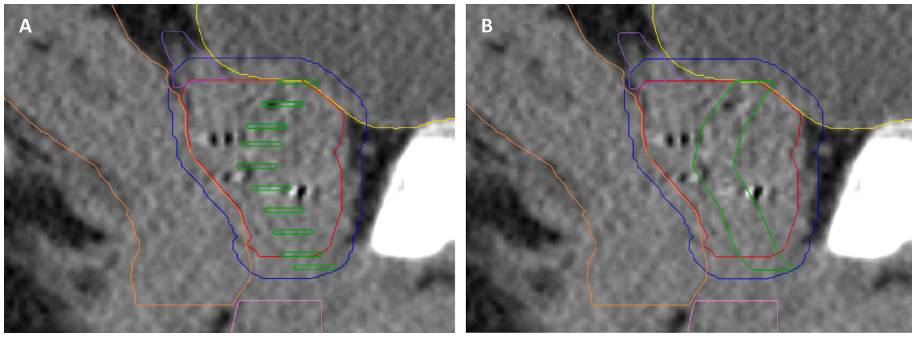

Fig. 2. CT planning scan demonstrating the surrogate urethra model development process. The script is first run on the treatment planning software and a 10mm diameter circle is placed along the prostate from 3/4 gland to apex. The 10mm circle at the prostate-bladder interface is manually contoured (A). The circles are then interpolated to form the surrogate urethra (B). Prostate CTV (red), seminal vesicle (purple), PTV (blue), surrogate urethra (green), rectum (orange), bladder (yellow), and penile bulb (pink). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

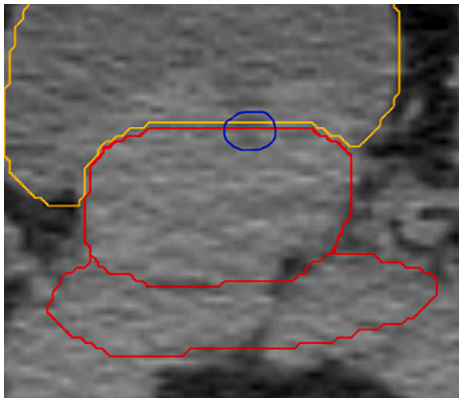

Fig. 3. Axial CT slice at the prostate-bladder interface. The blue contour demonstrates the urethra opening which can be visualised on CT imaging in some cases. Bladder (orange), prostate and proximal seminal vesicle (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Evaluating dosimetric performance of surrogate urethra

In order to evaluate the dosimetric performance of the surrogate urethra model, the differences between SUM and MDU for several dose parameters were tested for statistical significance using a paired *t*-test. These parameters include the D99, D98, average dose, D50, D2 and D1. The D(n) notation represents the dose in Gy received by a certain percentage (n%) of the urethra. For the paired *t*-test, a p-value of less than 0.05 was considered statistically significant. This analysis will allow us to assess how accurate the surrogate urethra model estimates urethra dose compared with the MRI-delineated 'true' urethra. A sample size calculation was performed for paired *t*-test analysis. Based on prior work from Bucci et al., we assumed a median difference in urethra dose volume parameters between the surrogate and true urethra of 4Gy [18]. We aimed for a 90% power and an alpha level of 0.05, resulting in a required sample size of 13. As a hypothesis generating study, we assessed the correlation between geometric performance metrics (e.g. DSC, HD, MDTA and UOS) and absolute difference in urethra dose volume parameters (e.g. D99, D98 etc) between the MDU and surrogate urethra, using the Spearman rank correlation coefficient. In view of multiple testing with the Spearman rank test, a pragmatic adjustment to the p-value threshold was made, in which a p-value of less than 0.01 was considered statistically significant. All analyses were completed using R, version 4.1.3 (R Studio, Boston, MA).

3. Results

A total of 34 MRI-delineated urethras were used to validate the surrogate urethra model. All patients in the study received a treatment dose of 36.25Gy in 5 fractions to the PTV, and 40Gy in 5 fractions to the CTV. When evaluating the geometric performance of the surrogate compared with the MDU, the median DSC was 0.32 (IQR 0.21–0.41), median HD was 8.4mm (IQR 7.1–10.1mm), median MDTA was 2.4mm (IQR, 2.2–3.2mm), and the median UOS was measured as 30% (IQR, 18–54%).

Table 1 provides a summary of the average urethra dose volume parameters for both the MDU and the SUM. When comparing the dose-volume parameters between the MDU and SUM, there was no statistically significant difference between D99, D98 and D95 (Table 1). The mean of differences between the SUM and MDU for the D50, D2 and D1

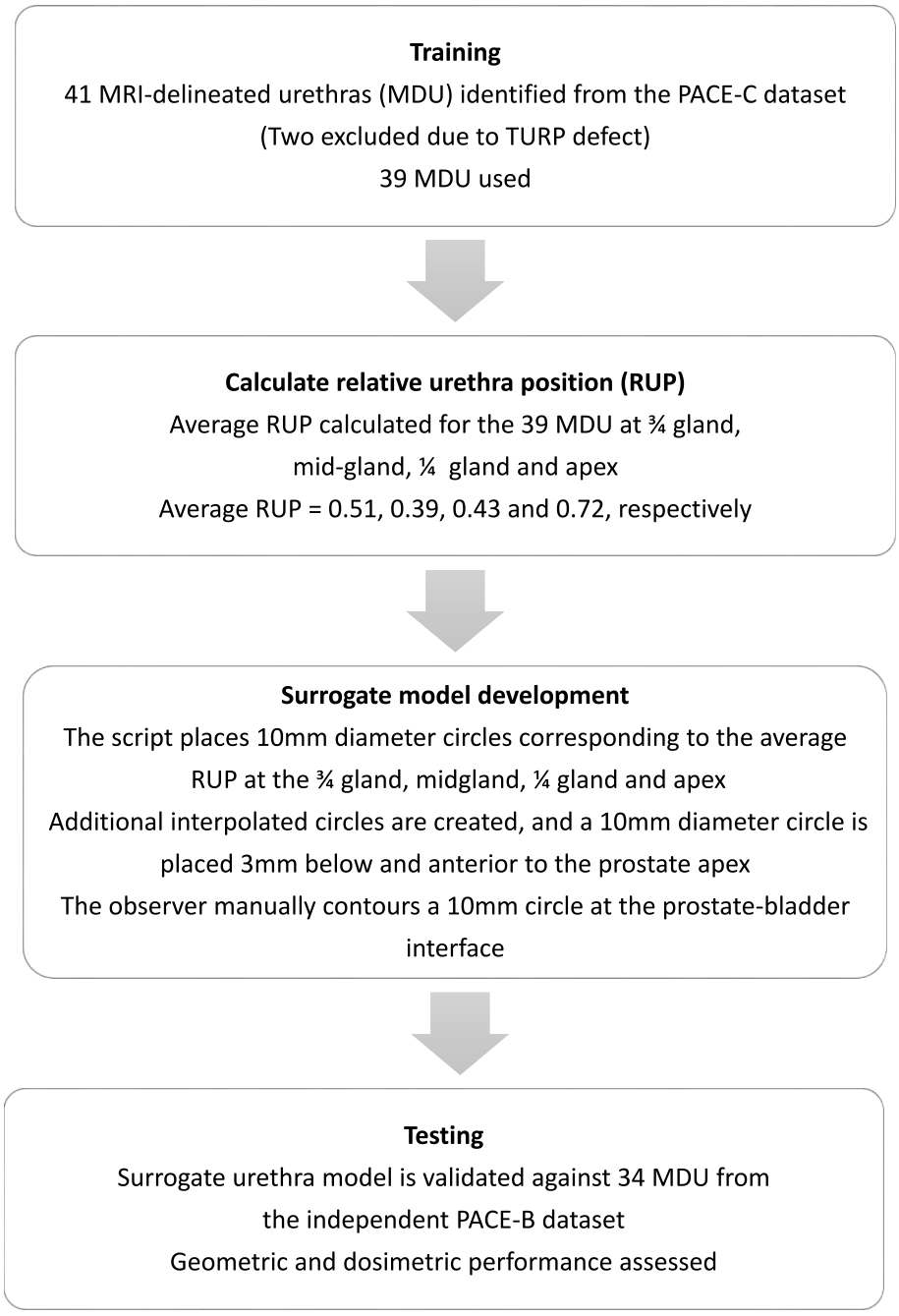

Fig. 4. Flowchart summarising the approach used to develop and validate the surrogate urethra model. TURP = transurethral resection of the prostate.

Table 1
Comparison between MRI-delineated urethra and surrogate urethra model dose-volume parameters.

Dose volume parameters	MRI-delineated urethra (n = 34)		Surrogate urethra model (n = 34)		Paired *t*-test	
	Mean (Gy)	Standard deviation	Mean (Gy)	Standard deviation	Mean of differences (95 % CI)	p-value
D99	39.21	1.39	39.33	1.18	−0.12 (−0.54 to 0.30)	0.57
D98	39.64	1.25	39.73	0.98	−0.09 (−0.46 to 0.27)	0.61
D95	40.32	0.94	40.43	0.94	−0.11 (−0.42 to 0.20)	0.46
Average	41.77	1.02	41.82	1.04	−0.04 (−0.13 to 0.04)	0.25
D50	41.86	1.10	41.93	1.11	−0.08 (−0.15 to −0.005)	**0.04**
D2	42.92	1.37	43.01	1.32	−0.09 (−0.18 to −0.01)	**0.02**
D1	43.01	1.36	43.12	1.34	−0.10 (−0.29 to −0.02)	**0.01**

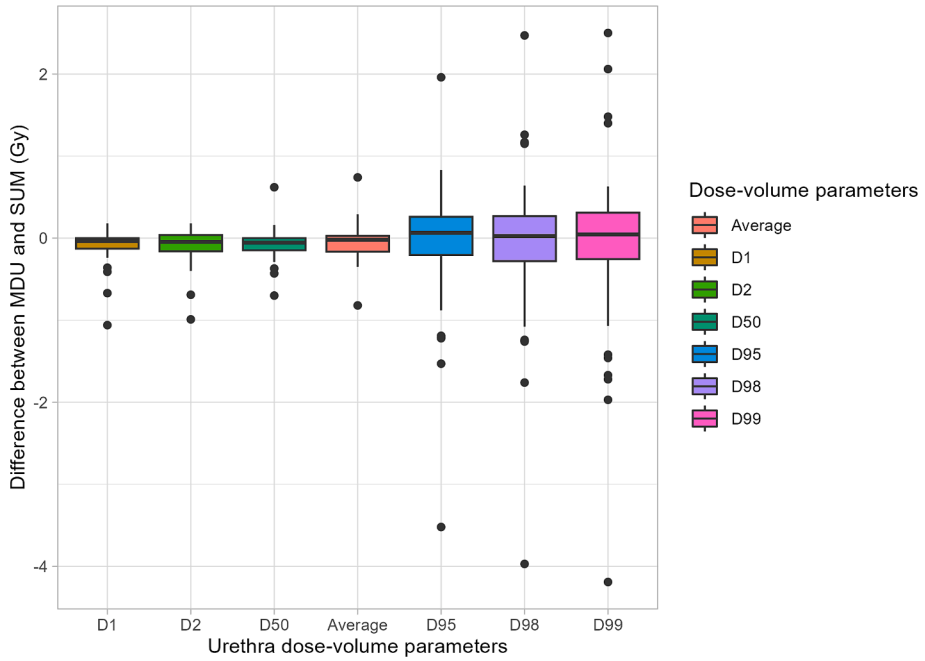

Fig. 5. Boxplot showing the difference in dose between the MRI-defined urethra and surrogate urethra for the different urethral dose-volume parameters. The D(n) notation represents the dose in Gy received by a certain percentage (n%) of the urethra.

were 0.08Gy (p=0.04), 0.09Gy (p=0.02) and 0.1Gy (p=0.01) respectively. Though these differences were statistically significant, they were not clinically significant. Fig. 5 provides a boxplot representation of the differences between urethra dose-volume parameters for the MDU and SUM.

Table 2 summarises the correlation between geometric performance measures and absolute differences in urethra dose-volume parameters between the SUM and MDU. There is no correlation between DSC, HD, MDTA and UOS, and absolute difference in D99, D98, D95, D2 and D1. However, there was a non-statistically significant moderate correlation between DSC (r=−0.32, p=0.06), HD (r=0.40, p=0.02), MDTA (r=0.32, p=0.06), UOS (r = 0.43, p=0.01) and absolute difference in D50. A statistically significant correlation was seen between absolute difference in average urethral dose and DSC (r=−0.45, p=0.007). There was a trend towards a correlation between absolute difference in average urethral dose and MDTA (r=0.39, p=0.02).

4. Discussion

We report our approach in developing and validating a simple urethra surrogate model to facilitate dose-toxicity modelling. When assessing the segmentation accuracy of the surrogate urethra, we achieved a median DSC of 0.32, median HD of 8.4mm, median MDTA of 2.4mm and a median UOS of 30%. While this would indicate significant geometric differences between our surrogate urethra model and the MRI-delineated urethra, there was no difference between the urethral D99, D98, D95 and average dose. We noted a statistically significant difference in urethral D50, D2 and D1, though the magnitude of difference was small. Leeman et al. demonstrated a correlation between maximum urethra dose metrics (MUDM) reported in 23 studies, and late urinary toxicity. They showed an increase in 1Gy to the MUDM corresponded to a 1% increased risk in late G2+ urinary toxicity [14]. As the mean of differences for the urethra dose-volume parameters were under 0.2Gy, we deemed them to not be clinically significant. Therefore, we concluded that although the SUM was not geometrically perfect, it was accurate enough to report dose to the urethra.

We demonstrated that standard metrics to assess segmentation accuracy have a moderate correlation between the absolute difference in urethra D50 and average urethral dose. We did not demonstrate a correlation between these metrics and differences in urethra D1/D2, likely because the absolute differences are small, and this study was not powered for this analysis.

However, the lack of correlation suggests that when assessing the segmentation accuracy of novel surrogates/auto-segmentation approaches, particularly where the volume in question is small, measuring differences in dose-volume parameters is essential. Several other studies have also demonstrated a poor correlation between common segmentation metrics and dosimetry [36–38]. Poel et al. showed in brain tumour patients, DSC correlated poorly with differences in Dmax (r=−0.13) and mean organ-at risk (OAR) dose (r=−0.11), and

Table 2
Correlation between geometric performance measures and absolute dose difference in urethral dose-volume parameters.

Dose volume parameters	Dice similarity co-efficient (DSC)		Hausdorff Distance (HD)		Mean distance to agreement (MDTA)		Percentage of MRI urethra outside surrogate (UOS)	
	Spearman's Rank (r)	p-value	Spearman's Rank (r)	p-value	Spearman's Rank (r)	p-value	Spearman's Rank (r)	p-value
D99	0.002	0.98	0.05	0.78	0.08	0.65	0.20	0.27
D98	−0.14	0.42	0.02	0.93	0.14	0.42	0.11	0.52
D95	−0.10	0.56	0.24	0.16	0.16	0.36	0.17	0.35
D50	−0.32	0.06	0.40	0.02	0.32	0.06	0.43	0.01
Average	**−0.45**	**0.007**	0.29	0.09	0.39	0.02	0.20	0.26
D2	−0.02	0.90	0.06	0.73	−0.04	0.81	−0.05	0.76
D1	−0.13	0.46	0.15	0.39	0.11	0.52	0.06	0.72

highlighted the need for better metrics that reflect how segmentation quality influence dosimetry [38].

Several alternative urethra surrogates have been proposed, mainly for prostate brachytherapy planning. Waterman et al. used the geometric centre of the prostate [19]. They demonstrated in 20 LDR-brachytherapy cases, a correlation in some urethral dose-volume parameters between the geometric centre surrogate and catheter-derived urethra. However, this model did not account for the anterior deviation of the urethra at the prostatic base; therefore, dose estimation is likely inaccurate in this region [19]. Nilsson et al. investigated the dosimetric consequence of using the geometric centre surrogate in HDR-brachytherapy planning. They showed statistically significant differences between dosimetric parameters and a catheter-derived urethra [29]. Bucci et al. showed a reasonable dosimetric correlation between the geometric centre surrogate and a deviated urethra surrogate against the gold-standard catheter-derived urethra [20]. It is unknown whether the deviated surrogate is translatable to external beam radiotherapy approaches, which tend to have more homogenous dose distribution than brachytherapy. Acosta et al. also proposed a multi-atlas-based segmentation (MABS) approach, which outperformed previously mentioned surrogates when measured using centreline distance from the catheter-derived urethra [22]. The metrics used to assess the segmentation accuracy differed from this study, and the MABS approach was trained using catheter-derived urethra. Recently, several studies have used machine learning methods, e.g., convolutional neural networks, to develop automated urethral segmentations; however, they are trained on MRI imaging [24,30,31]. These approaches show promise for MR-only based workflows; however, their use in CT-only workflows is limited. Cubero et al. recently developed a deep learning urethral segmentation (DLUS) model for CT planning scans, trained and compared with catheter-derived urethra. The DLUS had a smaller mean centreline distance (CLD) for the whole urethra than the MABS (1.6mm vs 3.3mm). However, when the DLUS was applied to 15 CT planning scans with urethras delineated using MRI, the mean CLD increased to 3.8mm [23]. Comparison to our study is difficult as different metrics were used to assess segmentation accuracy, and catheter-derived urethras were again used to train and validate the model. Studies, including this work, demonstrate that a urinary catheter can shift the urethra position, and therefore, there is still a need for urethra segmentation models for CT planning scans developed using urethras delineated by MRI [16,17].

There are several limitations with this study. Despite quality assuring the MRI-delineated urethras, accurate contouring on MRI can be challenging and there is significant inter-observer variability with urethra delineation. The training dataset uses a 2.5mm MRI planning scan slice thickness, and recent studies suggest inter-observer variability reduces with thinner MRI slices, which are often used with MR-guided radiotherapy [32]. Patients with TURP defects were not included in the surrogate model development, and therefore its application in this population is limited. There may also be more accurate methods to delineate the urethra without MRI. A recent study by Ong and colleagues demonstrated that urethral contouring using a CT-urethrogram has better agreement and less variability compared with T2-weighted MRI [35]. In our study, the DSC score was poor overall; however, DSC scores tend to be lower with smaller structures, and therefore other metrics such as MDTA, HD and UOS were used [33]. The surrogate model uses a larger diameter than the actual urethra diameter and, therefore, will encompass periurethral tissue and essentially acts as a urethra planning risk volume (PRV). However, the optimum urethra/PRV diameter is currently unknown. Zilli et al. published their outcomes following urethra-sparing prostate SBRT [34]. The urethra PRV in their study was defined using a urinary catheter followed by a 3mm isotropic expansion. The urethra PRV received a lower dose of 32.5Gy in 5 Fr, compared to the prostate and seminal vesicle (36.25Gy in 5Fr). The study demonstrated good 5-year biochemical relapse-free survival of 92.2–93%, suggesting a urethra-sparing approach is safe, assuming the urethra PRV diameter is approximately 8mm [34]. Our surrogate model can be used to estimate urethral dose on CT-planning scans; however, whether a 10mm diameter urethra surrogate is appropriate for urethra-sparing techniques is unknown. Due to the geometric differences, prospective utilisation of the surrogate in radiotherapy planning for urethral sparing approaches needs independent validation. Future work should focus on developing automated urethra segmentation approaches for CT-only workflow using machine-learning techniques trained using MRI-delineated urethras, as many radiotherapy centres globally lack MRI planning facilities. Work is ongoing to assess the correlation between urethra dose and late urinary toxicity following prostate SBRT.

5. Conclusion

We developed and validated a simple urethra surrogate model intending to estimate urethra dose to facilitate dose-toxicity analyses. While there were some geometric differences, the mean distance to agreement between the surrogate and MRI-delineated urethra was small at 2.4mm. We demonstrated no clinically significant difference in urethral dose-volume parameters between the surrogate urethra and MRI-delineated urethra. This surrogate could be validated in a larger cohort and then used to estimate urethra position on CT planning scans for dosimetric analysis in those without MRI planning scans or urinary catheters.

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CRediT authorship contribution statement

Ragu Ratnakumaran: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Jonathan Mohajer:** Methodology, Formal analysis, Writing – review & editing. **Samuel J. Withey:** Methodology, Writing – review & editing. **Douglas Brand:** Methodology, Writing – review & editing. **Ernest Lee:** Methodology, Writing – review & editing. **Andrew Loblaw:** Methodology, Writing – review & editing. **Shaun Tolan:** Methodology, Writing – review & editing. **Nicholas van As:** Methodology, Writing – review & editing. **Alison C. Tree:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ragu Ratnakumaran reports speaker fees from Accuray. Alison Tree reports research support from Elekta, Varian and Accuray, and honoraria/travel assistance from Elekta, Accuray and Janssen.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100769.

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