Voxel-based analysis for identification of urethro-vesical subregions associated with urinary toxicity after prostate cancer radiotherapy

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Project: RAMPART

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Purpose

To identify bladder and urethra subregions associated with urinary toxicity after prostate cancer radiotherapy based on voxel-wise statistical analysis. The proposed framework combines an accurate anatomical non-rigid registration approach for mapping the population 3D dose distributions to a single coordinate system and a voxel-wise analysis with respect to toxicity.

Materials and methods

Dataset: 272 localized prostate cancer patients treated with IMRT/IGRT from two multicentric prospective phase III trials (STIC- IGRT and PROFIT), were prospectively analyzed.

Study endpoints: For late toxicity at 5 years: dysuria grade ≥1, hematuria grade ≥1, retention grade ≥1, incontinence grade≥ 2 , frequency grade≥ 2 and global toxicity grade≥ 2. The endpoint for acute toxicity was grade ≥1 for all the symptoms.

Registration & Dose mapping : The registration algorithm, combined an affine followed by two nonrigid B-spline transformations. The obtained deformation fields were applied to wrap the planning doses to the template.

Dose-voxel maps & identification of subregions: Voxel-wise unirateral Mann-Whitney U tests were performed (alternative hypothesis: patients with toxicity received a higher dose), resulting in 3D maps for both dose differences and p-values. Threshold values of p=0.05 and p=0.01 were then applied to p-value maps to segment statistically significant sub-regions. The inverse transformations are used to propagate these sub-regions to the patent's native space.

Toxicity prediction: DVHs were computed for the bladder and the subregions and a univariate logistic regression model (at each dose bin) was used to predict the risk of 5-years GU toxicity.

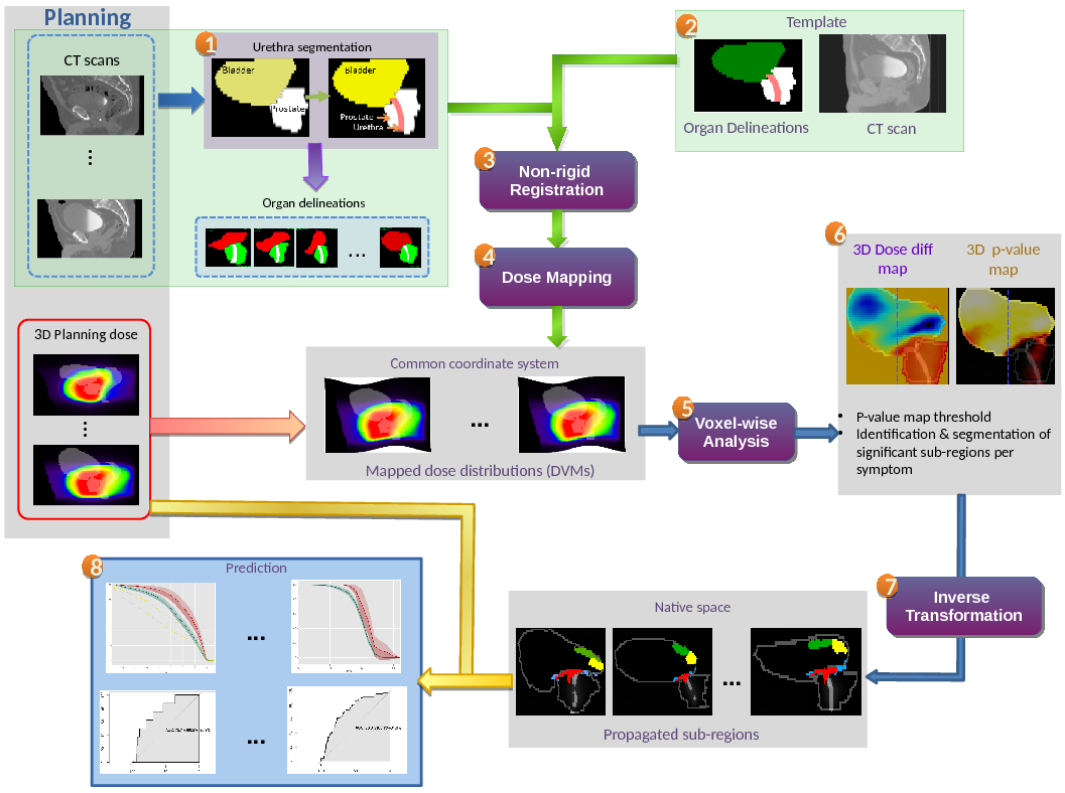

Figure 1. Flowchart of the method: I) urethra segmentation on the entire cohort, ii) template selection based on anatomic characteristics, iii) registration of the population to the template, iv) propagation of the dose distributions to the template, v)voxel-wise unirateral Mann-Whitney U tests, vi) identification of significant sub-regions per symptom, vii) propagation of the sub-regions from the template to the native space, viii) DVHs calculation and logistic regression at each bin.

Results

The median follow-up was 53 months. Associations of spatial dose measures to urinary toxicity were found to be dependent on specific symptoms (*Figure 2*). Clusters of statistically significant dose differences between the response groups were found in the posterior and inferior region of the bladder, laterally to the trigone and trigone itself and the urethra. At the native space the mean dose difference for these symptoms remain significant. The prediction capabilities of sub-regions DVH were always higher compared to those of the bladder's DVH (*Table 1*).

	Incontinence (acute, n=6%)		Incontinence (late, n=8%)		Frequency (n=22%)		Retention (n=50%)		Dysuria (n=21%)		Global Tox. (n=48%)	
	Sub-region	Bladder	Sub-region	Bladder	Sub-region	Bladder	Sub-region	Bladder	Sub-region	Bladder	Sub-region	Bladder
Tox. Pts (mean dose + std)	79.65 ± 1.41	31.28 ± 6.53	79.11 ± 0.99	36.28 ± 13.44	78.63 ± 1.88	38.64 ± 12.0	36.34 ± 16.46	46.0 ± 13.93	65.35 ± 7.06	50.12 ± 10.12	78.31 ± 2.18	37.0 ± 14.38
Non-tox. Pts (mean dose + std)	78.39 ± 1.55	35.71 ± 14.72	77.22 ± 2.40	40.37 ± 13.12	77.69 ± 1.76	40.48 ± 13.52	27.06 ± 13.13	41.59 ± 12.52	56.83 ± 9.95	40.77 ± 12.95	77.81 ± 1.30	39.55 ± 13.08
p-value	0.01	0.86	<0.01	0.78	0.013	0.75	<0.01	0.037	<0.01	<0.01	<0.01	0.85
Logistic Regresion (DVH)												
RR (Relative Risk)	1.05 (1.02 - 1.09)	NS	1.04 (1.01-1.07)	1.21 (1.05-1.41)	1.02 (1.01-1.04)	1.3 (1.04-1.64)	1.02 (1.01 -1.04)	NS	1.06 (1.02 - 1.09)	1.04 (1.01 - 1.07)	1.02 (1.01 - 1.03)	1.38 (1.05 - 1.8)
AUCmax (Vx)	70.9 (V81)		65.7 (V80)	71 (V81)	59 (V81)	68 (V37)	78.7 (V53)		68 (V79)	65.2 (V80)		
P-val of AUCmax	<0.01		0.01	<0.01	0.02	<0.01	<0.01		<0.01	0.018		

Table 1. Results of statistical analysis (upper half) and logistic regression (lower half) at the native space.

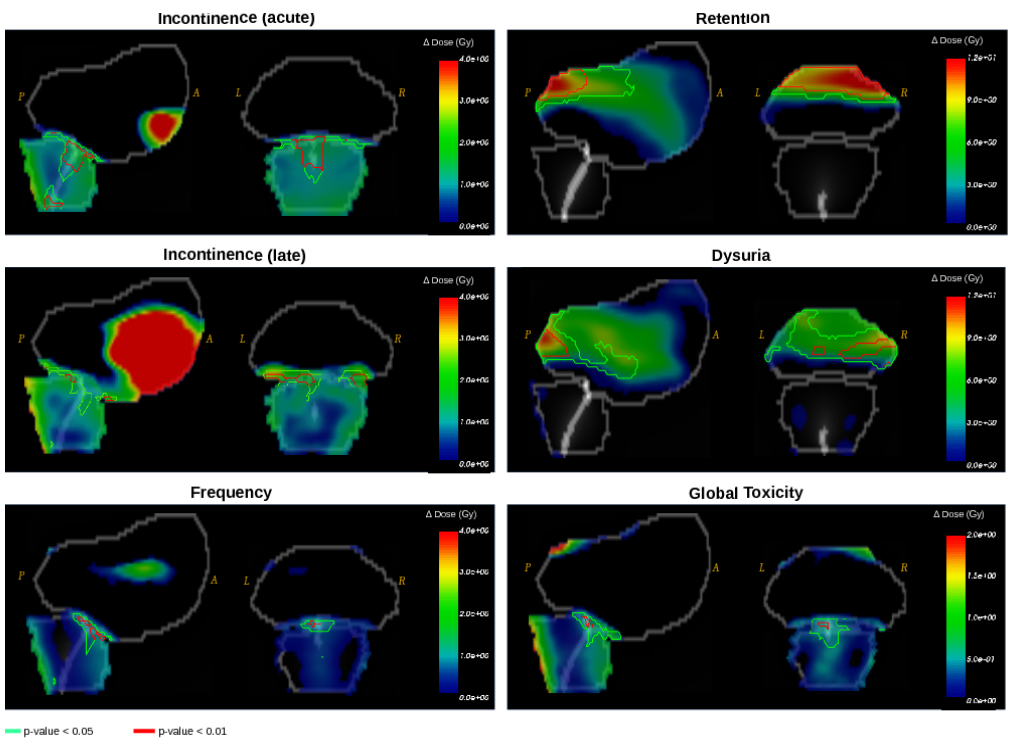

Figure 2. Visualisation of the results on 2D slices of the maps: sagittal and coronal planes of the between-group dose differences (only positive difference is shown), for each symptom, accompanied by the regions of statistical significance (green for p< 0.05 and red for p< 0.01). Abbreviations: A=anterior; P=posterior; R=right; L=left.

Conclusion

We implemented a framework including a robust registration process and a VB approach to investigate the local dose-urinary toxicity relationship. The dose delivered to the posterior and inferior region of the bladder, laterally to the trigone and trigone itself and the urethra is predictive of specific urinary symptoms. However, further confirmation on larger cohorts is need.