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A prospective comparison of the effects of interfractional variations on proton therapy and IMRT for prostate cancer

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Abstract

Purpose—To quantify and compare the impact of interfractional setup and anatomy variations on proton therapy (PT) and intensity modulated radiotherapy (IMRT) for prostate cancer.

Methods and Materials—Twenty patients with low- or intermediate-risk prostate cancer randomized to receive passive-scattering PT (n=10) and IMRT (n=10) were selected. For both modalities, clinical treatment plans included 50.4 Gy(RBE) to prostate and proximal seminal vesicles, and prostate-only boost to 79.2 Gy(RBE) in 1.8 Gy(RBE) per fraction. Implanted fiducials were used for prostate localization, and endorectal balloons for immobilization. Patients in PT and IMRT arms received weekly CT and cone-beam CT (CBCT) scans, respectively. The planned dose was re-calculated on each weekly image, scaled and mapped onto the planning CT using deformable registration. The resulting accumulated dose distribution over the entire treatment course was compared with the planned dose using dose-volume histogram (DVH) and gamma analysis.

Results—The target conformity index remained acceptable after accumulation. The largest decrease in the average prostate D_{98} was 2.2 and 0.7 Gy for PT and IMRT, respectively. On average, the mean dose to bladder increased by 3.26 ± 7.51 Gy and 1.97 ± 6.84 Gy for PT and IMRT, respectively. These values were 0.74 ± 2.37 and 0.56 ± 1.90 for rectum. Differences between changes in DVH indices were not statistically significant between the two modalities. All volume indices remained within the protocol tolerances after accumulation. The average pass rate in gamma analysis, assuming tolerances of 3 mm and 3%, for PT/IMRT for CTV, bladder, rectum and whole patient were 100/100, 92.6/99, 99.2/100 and 97.2/99.4, respectively.

Conclusion—The difference in target coverage and OAR dose deviations for PT and IMRT was not statistically significant under the guidelines of this protocol.

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1. Introduction

Prostate adenocarcinoma is one of the most prevalent types of cancer. According to the surveillance, epidemiology and end result program (SEER), 220,800 men are estimated to be diagnosed with prostate cancer in the United States in 2015 [1]. External beam radiation therapy, e.g. intensity modulated radiotherapy (IMRT) and proton therapy (PT), is an important treatment option for this patient group. Although PT, in principle, has the potential to reduce patient toxicities by reducing the dose to normal tissue due to its steep dose gradients, it could be more vulnerable than IMRT to delivery uncertainties, hence requiring the use of limited beam angles and larger volumes treated to high dose [2, 3]. On the other hand, IMRT irradiates a larger volume of patient tissue with a lower dose bath, while delivering a rather conformal high-dose to the target with less steep gradients. Common toxicities observed for both types of radiation include rectal, bowel, urinary and sexual dysfunctions that could significantly impair the patient's quality of life.

In effort to compare the efficacy of proton and photon-based radiotherapy for prostate, studies have found that while IMRT offers reduced high dose (>60 Gy) to the bladder compared with PT, substantially larger volume of healthy organs receives lower dose (<50 Gy) [4–10]. So far, there has been no clear indication of long-term benefits of PT compared to IMRT [2].

Aside from dosimetric differences between the two modalities, other aspects e.g. the effect of inevitable motion on the delivered dose, are crucial to address [11–13]. Intra- and interfractional motion patterns of the prostate have been thoroughly studied [14–16]. As for the dosimetric consequences of motion, early work by Zhang *et al* compared the impact of anatomy and setup changes, on PT and IMRT by re-calculating the dose on repeat CT scans and assessing the organ dose on each image [17]. Soukup *et al* studied the sensitivity of PT and IMRT to organ movement for 4 patients based on a non-clinical setup scheme [18]. XXX *et al* assessed the effect of anatomy variations on PT, assuming ideal setup. While these initial studies are valuable, it is important to consider the latest realistic clinical treatment settings and alignment strategies, and understand the cumulative effect of variations over the course of treatment to accurately compare the robustness and expected toxicities between the modalities as clinically delivered.

This study is based on the patient data from an ongoing randomized clinical trial, prospectively reporting on the impact of interfractional setup and anatomy variations on passive-scattering PT vs. IMRT using a standardized clinical protocol. We used serial imaging data to identify the patient variations and calculate the dosimetric consequences. We hypothesize that both modalities are affected by uncertainties and there is no clear disparity in the sign/direction and size of the effect on commonly evaluated dose-volume metrics. This work is not only imperative for a critical comparison of treatment efficacy between the two modalities, but could also provide guidelines on the required motion control techniques for successful treatments of prostate cancer.

2. Methods and Materials

2.1. Patient Selection and Prescription

Twenty patients, ten randomized to passive-scattering PT and ten to IMRT, participating in a clinical trial in our institution, who consented to undergo an optional imaging study were included, with no further selection criteria. All patients had low- or intermediate-risk prostate cancer with clinical stages T1c to T2b, Gleason scores of less than or equal to 7, and PSA of less than 20.

The target volumes were defined as CTV7920 being the whole prostate gland and CTV5040 the prostate plus 5–10 mm (low-risk disease) or 10–15 mm (intermediate-risk disease) of the proximal seminal vesicle tissue. Both CTVs were expanded by 5 mm (4 mm posterior) to form the corresponding PTVs. For both modalities, the prescription dose was 79.2 Gy(RBE) to CTV7920 and 50.4 Gy(RBE) to CTV5040, in 1.8 Gy(RBE) fractions. Organs at risk (OARs) included the bladder, anterior rectal wall, whole rectum, penile bulb and the bilateral femoral heads.

2.2. Treatment Planning and Delivery

The treatment plans were created by clinical dosimetrists using the XiO (Elekta, Stockholm, Sweden) and RayStation (RaySearch Laboratories, Sweden) planning systems for PT and IMRT, respectively. Proton plans included bilateral beams, using 1.0–1.2 cm aperture expansion from the PTVs, 3.5% range uncertainty margin, and 1 cm range compensator smearing. The IMRT plans included seven coplanar fields at 0 (AP), 60, 100, 135 (left oblique), 225, 260 and 300 (right oblique) degree angles. Multicriteria optimization was used for IMRT plans [19]. The minimum planning constraints for coverage and OAR dose were defined by the protocol and listed in table 3.

Proton treatments were delivered by an IBA (IBA Inc., Louvain La Neuve, Belgium) double-scattering gantry system and IMRT treatments were delivered using an Elekta Infinity linac with an on-board kV X-ray volumetric imaging system (Elekta, Crawley, UK). Patient setup and target localization were achieved by matching three implanted gold-coil fiducial markers, using orthogonal x-ray radiographs before PT and cone-beam CT (CBCT) imaging prior to IMRT treatment. The clinical setup tolerances were 1-mm translational and 1-degree rotational difference between simulation and treatment (fiducial and bony) landmarks. Patient immobilization was achieved by using leg/pelvis support as well as water-filled (60 ml) endorectal balloons, as previously found to be an effective immobilization strategy [20]. Furthermore, participants were instructed to undergo treatment with a comfortably full bladder and empty bowel.

2.3. Serial Imaging

Imaging series consisted of 9 data sets per patient, one for each week of treatment. Proton patients received weekly CT scans on a GE RT16 simulator (GE Healthcare, Waukesha, WI - the same scanner as used for their simulation) shortly prior or following their treatment. This timing was variable for each patient and treatment day, depending on the simulator availability. Care was taken for the patient positioning, balloon insertion and leg

immobilization to be identical between the serial scans and treatment. The image resolution was $0.98 \times 0.98 \text{ mm}^2$ with 1.25–2.5 mm slice thickness (finer slices at the target position, as in simulation CT). The IMRT patients received daily CBCT as part of treatment setup, and an extended scan of enhanced quality, once a week, which had a higher resolution ($1 \times 1 \times 1 \text{ mm}^3$), a larger field of view, and used additional filters to reduce artifacts.

2.4. Dose Analysis

To estimate the dose that was actually delivered, taking the setup and anatomy variations into account, the treatment plan was applied and dose was re-calculated on each of 9 serial images, and scaled to $1/9^{\text{th}}$ of the total plan dose. The weekly dose distributions were then transferred back onto the planning CT and added by means of deformable dose accumulation (MiM-6.4), allowing for direct comparison with the planned dose. For IMRT patients, a technique was developed and fully validated to enable weekly dose re-calculation using the CBCT data [21]. In this method, the planning CT was deformed using Plastimatch image registration software [22] to each of the weekly CBCT images (landmark assistance was utilized when large bladder volume changes were present) and the deformed CT images were then used for weekly dose re-calculation.

For all patients, the serial images were rigidly registered to the planning CT prior to dose recalculation, by aligning the fiducial markers, similarly to the clinical setup satisfying clinical tolerances. In the PT arm, this registration included rotations defined by bony-anatomy landmarks in coccyx, iliac crest and pubic symphysis, in addition to the translation defined by average marker positions. For IMRT, no rotation was included in the setup as currently practiced in our institution.

Finally, the accumulated and planned dose distributions were compared via dose-volume histogram (DVH) indices, i.e. D_{mean} , D_{98} , D_2 (mean dose and dose at 98 and 2% of total volume), and V_x (volume at x Gy dose). Additionally, the equivalent uniform dose (EUD) [23] as well as tumor control probability (TCP) and normal tissue complication probability (NTCP) were assessed [24–27]. Model parameters were taken from the literature [24]. The conformity index (CI) was also derived as defined by the RTOG ($\text{CI} = V_{7920}/V_{\text{CTV}7920}$) [28]. Gamma analysis of the total dose distribution was performed at the tolerance level of 3%/3mm for the $\gamma < 1$ test, within the region with dose $> 10\%$ of the maximum dose [29].

2.5. Statistical Analysis

Differences between PT and IMRT dose-volume index deviations (accumulated–planned dose) were tested for statistical significance by performing Mann-Whitney U-test using R statistics software [30].

3. Results

3.1. Patient Variations

The patient setup and anatomy changes during the treatment course were in general non-negligible. Although setup variations were minimized through the use of implanted fiducials and image-guidance, uncertainties due to prostate rotations or deformations remained.

Anatomy variations included bladder volume, rectal filling, and balloon insertion inconsistencies, femoral head rotations and immobilization of soft tissue (changes in the external contour). Table 1 summarizes the average variations relative to the planning CT for PT and IMRT patients. There was no significant difference in the degree of captured variations between the two patient groups. The seed-bone shift refers to the absolute 3-dimensional translation of the weekly CT registered to the simulation CT by bony-anatomy vs. fiducial alignment, as a measure of changes in relative position of the prostate and the bones, caused by prostate migration/deformation or bony-anatomy misalignments between simulation and treatment. This was on average 4.7 and 3.2 mm for PT and IMRT patients, respectively. The average weekly bladder volume was generally smaller than the volume at the time of simulation by 63.6 (median) and 588.8 (maximum) cc for PT, and 54.3 (median) and 453.9 (maximum) cc for IMRT. For PT patients, however, these volumes might have been slightly different at the time of treatment since the weekly CT scans were performed, typically, between 60 and 30 minutes before or after treatment. The prostate volume ranged from 24 to 84 cc, median 45.5 cc. Figure 1 illustrates an example of differences in patient anatomy between the simulation CT and two non-consecutive weekly scans for PT and IMRT patients. Anatomy variations are clearly identifiable on the CT/CBCT images. Pre-treatment assessment of the serial images for both modalities did not readily indicate a need for treatment adaptation in any instance.

3.2. Impact of patient variations on dose

Figure 2 features planned and accumulated dose distributions for representative patients in PT and IMRT arms. The DVH curves for the CTV7920 and OARs are also displayed. We found that the target dose is generally consistent between planned and accumulated distributions for both modalities. Target underdose was more prevalent for PTVs as expected, since they are specifically designed to protect the CTV against the loss of coverage, and the induced dose decrease in these structures outside of clinical targets might not be of concern. As seen in the DVH curves, the bladder dose understandably showcased the most variability among all OARs due to the susceptibility to volume changes. The rectum dose showed some variations as a result of general soft tissue deformations, gas pockets between the balloon and rectal wall, and residual rectal filling.

Table 2 quantifies the differences between planned and accumulated dose-volume indices for all targets and OARs averaged over all patients. The standard deviations of the population as well as p-values to evaluate the significance of the differences between PT and IMRT are also listed. As expected the target dose was on average more conformal for IMRT (CTV7920 $CI_{Average}=1.9$) than PT (CTV7920 $CI_{Average}=2.5$). The average CI decreased by 0.19 and 0.06 units for PT and IMRT, respectively after accounting for the setup/anatomy variations, but remained well above the tolerance of 1 in all cases. The average target D_{98} was comparable between modalities but more spread out for IMRT than PT, except CTV7920 where the standard deviation was smaller for IMRT than PT. The standard deviation band was larger for PTVs than CTVs. In the most extreme case, the average prostate D_{98} decreased by 2.2 (patient 10) and 0.7 Gy (patient 1) for PT and IMRT, respectively. The largest reduction in average prostate D_{mean} was 0.7 Gy for both modalities. Regarding the seminal vesicles coverage, the largest reduction in D_{98} for CTV5040 was 1.9

and 6.6 Gy for PT and IMRT, respectively. The average prostate TCP was 93.5% for both modalities and the differences between planned and accumulated dose were negligible. The average and standard deviations of the changes in bladder D_{mean} was slightly larger for PT (3.26 ± 7.51 Gy) than IMRT (1.97 ± 6.84 Gy). The EUD difference was comparable at 1.23 ± 5.83 Gy for PT and 1.78 ± 6.09 Gy for IMRT. For rectum, the D_{mean} deviations were below 0.8 Gy for both modalities. For all OARs, the average parameter changes were not statistically significantly different between modalities. The differences in NTCP changes were negligible ($<0.3\%$) for all OARs between modalities. The gamma-index passing rate for all targets and all patients was 100%. The average passing rate for PT/IMRT considering the bladder, rectum and whole-body was 92.6/99.0%, 99.2/100.0% and 97.5/99.4%, respectively.

The most extreme cases of bladder mean dose increase (>8 Gy) occurred for PT patients 3 and 10, and IMRT patients 4, 7, 9 and 10, due to the combination of consistently empty bladder at the time of treatment and a large (>4 mm) displacement between fiducials and the bony-anatomy in simulation and weekly images. The largest increase in rectal D_{mean} was 3.8 Gy for PT (patient 10) and 3.4 Gy for IMRT (patient 3).

Table 3 summarizes the average and standard deviation of the volume indices and the respective protocol guidelines. It shows that for all cases, even ones with relatively large variations, the target coverage remains per protocol, except for one PT case (patient 10) where V77.6 for CTV7920 was 1.8% below the tolerance (see discussion). The PTV7920 coverage deviated from the protocol guidelines in several cases after accumulation for both modalities, which was not of clinical concern as previously discussed. For bladder, rectum and femoral heads, all indices remained below the maximum protocol constraints after accumulation for both modalities.

4. Discussion

This work presented a comprehensive analysis of the impact of interfractional motion on PT vs. IMRT using prospective patient data, and clinically common treatment settings and setup/immobilization techniques. Weekly serial imaging data was acquired from twenty patients. The results of our analysis showed no significant difference in susceptibility of target coverage loss and nearby-tissue overdose due to variations, between PT and IMRT, supporting our initial hypothesis. The maximum loss in prostate D_{98} was 2.2 Gy for PT and 0.7 Gy for IMRT, whereas the maximum increase in average OAR D_{mean} was 20.0 and 15.2 Gy for bladder for PT and IMRT, respectively. Relatively large target underdose happened for proton patient 10, whose prostate was substantially rotated during treatment compared to the simulation. Since, during alignment, rotation is typically applied with respect to the bony-anatomy rather than the fiducials, all fiducials could not be aligned simultaneously. The same patient also presented with systematically smaller bladder size at the time of treatment compared to simulation, which could be one reason for the observed prostate rotation. The largest dose discrepancies happened in week 2, when the absolute observed seed-bony shift was 11 mm. As for IMRT, the loss of target coverage for patient 1 can be explained by the consistent rectal gas trapped in the anterior side of the balloon, which caused slight deformation of the prostate and dislocation of the most posterior fiducial.

Our findings were consistent with and complementary to the conclusions of previous retrospective studies, which claimed prostate PT is generally robust to interfractional anatomy variations, and improved control could be achieved by maintaining consistent patient anatomy and using immobilization devices [11, 12], and also that with the help of improved immobilization, PT and IMRT are similarly insensitive to interfractional motion [17, 18]. XXX *et al* noted the subcutaneous adipose tissue and femur rotation to be contributing factors to dose deviations in PT with lateral fields [11]. XXX *et al* found the primary source of dose discrepancy to be excessive rectal gas in the absence of rectal immobilization [12]. In comparison, the use of endorectal balloons in our study proved effective in preventing large prostate motion due to rectal gas. The main causes of dose degradation found here were inaccuracies in fiducial-based patient alignment due to possible prostate rotation/deformations or large bladder filling inconsistencies. The most affected was patient 10 as described above.

In attempt to further characterize the source of discrepancies between the planned and accumulated dose distributions, relevant anatomical changes were correlated with the differences in dosimetric indices for the target and OARs. Figure 3 illustrates examples of such correlations. The degree of correlations was patient-dependent and some correlations were not strong due to possible coupling of factors effecting these variations. For example, a relation between reduction of PTV7920 D_{98} and increase in the overall changes between fiducial vs. bony-anatomy alignment was found for both modalities. The CTV7920 coverage was sufficient and constant throughout the treatment, except for patient 10 where it strongly correlated ($R^2=0.82$) with seed-bony shift and absolute average rotation of the femoral head with respect to their initial setup position. The percent difference in bladder D_{mean} increased with decreasing bladder size at the time of treatment compared to simulation, which was slightly more apparent for PT. Bladder D_{mean} was also correlated with the shift between fiducial- and bony-anatomy-based alignments in the anterior-posterior (AP) direction. This shift might be partly dependent on the bladder size but is also affected by other factors e.g. prostate rotations, posterior seed displacement by residual rectal gas, etc. The AP shift also had a small effect on the rectal D_{mean} opposite to that of the bladder. Inconsistencies in rectal balloon insertion angle did not correlate with either target underdose or increased exposure of the anterior rectal wall. No other significant relations were found.

Although the data collection technique was optimized to allow for achieving the study goals with maximum accuracy, some inherent limitations existed. One such limitation was the unavailability of 3D image-guidance at the time of treatment for PT, thus preventing serial images to be taken at the time of treatment, leading to slight differences between anatomy at the time of imaging and treatment (e.g. bladder size), which could effect how closely the accumulated dose resembled the actual delivered dose. For IMRT, small uncertainties in recalculated dose ($<2\%$) might be introduced due to the finite accuracy of the CT-CBCT deformable registration [19, 22]. Furthermore the study sample size was limited. However, as documented in prior publications, comparable sample sizes were sufficient to identify notable and significant differences between treatments [4, 31, 32].

Although this study focused specifically on passive scattering PT since it has been the primary PT modality for the trial up to this point, pencil beam scanning (PBS) PT is of

increasing interest for prostate radiotherapy. Hence, a future goal would be to examine the robustness of PBS delivery. With the anticipated improvements in PT technology in the near future, e.g. availability of PBS and routine in-room 3D image-guidance in more facilities leading to possible planning margin reduction, the topic of robustness might need to be revisited in a protocol-specific manner.

5. Conclusion

Although interfractional variations are non-negligible for patients undergoing external beam radiation therapy for prostate cancer, the impact on dose degradation for targets and OARs was not of clinical concern for cases studied due to improved setup, immobilization and robust planning techniques, and the differences between PT and IMRT were not statistically significant. Although dose deviations were not clinically significant, it is still desirable that anatomic variations, e.g. bladder, be further reduced via more strict monitoring and patient-compliance requirements. Therefore we conclude that by following the guidelines set forth by the protocol the impact of the interfractional motion could be effectively minimized for both modalities.

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Figure 1.
Variations for selected patients: rectal filling (top), bladder volume (middle), fiducial position relative to bony-anatomy (bottom), and their effect on weekly dose.

Figure 2. Dose distributions comparing PT and IMRT, and DVHs for planned (solid) vs. accumulated (dashed) dose. Asterisks show the organ-specific constraints.

Figure 3.
Correlations between anatomy and setup variations with organ dose changes.

Table 1

Patient specifications and variations relative to the planning CT: pre-treatment prostate volume, average weekly seed-bony-anatomy shift relative to simulation, average bladder volume variations, average difference in absolute bilateral femoral head rotation and average rectal balloon insertion angle for all PT and IMRT patients. Average values (Av) are also shown for each modality.

	PT					IMRT				
	Prostate volume [cc]	Seed – bone shift [mm]	Bladder variation (weekly-sim) [cc]	Femoral head rotation [deg]	Balloon angle [deg]	Prostate volume [cc]	Seed – bone shift [mm]	Bladder variation (weekly-sim) [cc]	Femoral head rotation [deg]	Balloon angle [deg]
1	40.6	1.9	1.1	2.8	0.9	45.0	2.1	-103.9	3.1	-1.1
2	24.0	3.7	-14.4	2.2	-1.3	72.2	1.8	-34.9	0.7	-2.7
3	38.2	6.2	-102.0	2.1	-0.6	33.1	3.9	-40.4	2.0	-6.2
4	26.2	5.8	23.4	1.6	-3.5	34.1	5.0	-160.0	0.5	1.2
5	57.0	3.6	-150.6	0.2	-2.4	34.6	2.2	44.0	3.7	0.3
6	68.7	6.2	-153.5	7.7	-0.7	55.7	2.4	-2.9	2.9	-4.3
7	45.9	2.7	44.3	3.9	-0.8	56.1	1.6	-453.9	5.3	-2.7
8	58.3	5.9	-35.2	0.9	-4.2	31.0	3.1	-11.0	2.9	-3.7
9	35.6	5.2	-153.2	0.4	0.4	60.2	4.1	-68.2	3.4	-11.2
10	84.3	6.2	-588.8	4.0	2.8	67.5	5.8	-124.4	1.2	2.9
Av	47.9	4.7	-112.9	2.6	-0.9	49.0	3.2	-95.6	2.6	-2.8

Table 2

Average and standard deviation of differences between accumulated and planned DVH indices, comparing PT and IMRT. Negative values indicate decreased accumulated parameters. None of the differences are statistically significant ($p < 0.05$).

Modality		PT		IMRT		p-value		Modality		PT		IMRT		p-value	
Organs/Indices								Organs/Indices							
CTV7920	CI	-0.19 ± 0.20		-0.06 ± 0.24		0.32		Bladder	Dmean [Gy]	3.26 ± 7.51		1.97 ± 6.84		0.85	
	D98 [Gy]	-0.23 ± 0.71		0.01 ± 0.46		0.85			D2 [Gy]	-1.32 ± 1.49		1.30 ± 5.87		0.25	
	D2 [Gy]	-0.22 ± 0.30		-0.17 ± 0.72		0.39			V75 [%]	-0.91 ± 1.84		0.20 ± 3.11		0.22	
	Dmean [Gy]	-0.10 ± 0.24		0.07 ± 0.64		0.85			V70 [%]	-0.81 ± 2.70		0.45 ± 3.84		0.14	
	V79.2 [%]	-1.25 ± 3.60		-1.76 ± 2.22		1.00			V55 [%]	0.82 ± 6.40		1.61 ± 6.13		0.44	
	V77.6 [%]	-0.28 ± 0.88		-0.04 ± 0.11		1.00			V45 [%]	2.61 ± 9.27		2.13 ± 8.33		0.79	
	EUD [Gy]	-0.10 ± 0.25		0.07 ± 0.63		0.79			EUD [Gy]	1.23 ± 5.83		1.78 ± 6.09		0.74	
	TCP [%]	-0.03 ± 0.09		0.02 ± 0.22		0.79			NTCP [%]	0.01 ± 0.02		0.00 ± 0.00		0.85	
CTV5040	D98 [Gy]	-0.04 ± 1.02		-0.08 ± 3.02		0.91		Rectum	Dmean [Gy]	0.74 ± 2.37		0.56 ± 1.90		0.91	
	D2 [Gy]	-0.22 ± 0.30		-0.14 ± 0.74		0.53			D2 [Gy]	-0.81 ± 1.11		-0.44 ± 1.91		0.53	
	Dmean [Gy]	-0.10 ± 0.20		0.07 ± 0.72		0.68			V75 [%]	-0.75 ± 0.96		0.24 ± 1.68		0.22	
	V50.4 [%]	0.00 ± 0.00		0.00 ± 0.00		-			V70 [%]	-0.85 ± 1.21		0.37 ± 2.04		0.28	
	EUD [Gy]	-0.02 ± 0.22		0.02 ± 0.89		1.00			V50 [%]	-0.42 ± 2.29		0.73 ± 2.91		0.58	
	TCP [%]	-0.01 ± 0.08		0.00 ± 0.32		1.00			V40 [%]	0.06 ± 2.94		0.85 ± 3.34		0.91	
	D98 [Gy]	-1.7 ± 2.49		-2.83 ± 3.32		0.25			EUD [Gy]	-0.93 ± 1.29		0.10 ± 2.15		0.35	
	D2 [Gy]	-0.28 ± 0.25		-0.17 ± 0.77		0.85			NTCP [%]	-0.09 ± 0.16		0.08 ± 0.30		0.32	
PTV7920	Dmean [Gy]	-0.29 ± 0.46		-0.22 ± 0.62		0.85		ARW*	Dmean [Gy]	1.14 ± 1.89		0.84 ± 2.62		0.91	
	V77.6 [%]	-2.65 ± 3.18		-3.94 ± 3.44		0.22			D2 [Gy]	-0.36 ± 0.44		-0.29 ± 0.65		0.97	
	EUD [Gy]	-0.54 ± 1.11		-0.75 ± 1.32		0.48			EUD [Gy]	-0.50 ± 0.73		-0.12 ± 1.84		0.53	
	D98 [Gy]	-0.38 ± 2.51		-0.40 ± 6.79		0.97			Dmean [Gy]	0.43 ± 0.60		0.09 ± 0.65		0.44	
	D2 [Gy]	-0.23 ± 0.32		-0.15 ± 0.78		0.79			D2 [Gy]	1.99 ± 2.95		0.26 ± 1.62		0.11	
PTV5040	Dmean [Gy]	-0.27 ± 0.33		-0.19 ± 1.02		0.79		PRW**	EUD [Gy]	1.92 ± 2.88		0.22 ± 1.23		0.12	

Modality	PT	IMRT	p-value	Modality	PT	IMRT	p-value
Organs/Indices		Organs/Indices		Organs/Indices		Organs/Indices	
R. femoral head	V49.4 [%]	0.00 ± 0.02	0.69	R. femoral head	Dmean [Gy]	0.11 ± 0.38	0.09
	EUD [Gy]	-0.30 ± 0.90	0.91		D2 [Gy]	-1.70 ± 1.79	0.08
L. femoral head	Dmean [Gy]	-0.01 ± 0.81	0.44	L. femoral head	V45 [%]	0.00 ± 0.00	-
	D2 [Gy]	0.00 ± 0.34	0.11		EUD [Gy]	-0.45 ± 0.59	0.35
Penile bulb	V45 [%]	0.00 ± 0.00	-	Penile bulb	Dmean [Gy]	1.29 ± 8.22	0.85
	EUD [Gy]	-0.24 ± 0.32	1.00		D2 [Gy]	-4.76 ± 10.34	0.97

*ARW: Anterior rectal wall,

**PRW: Posterior rectal wall

Table 3
Average and standard deviation of volume indices (%) compared to the tolerance per protocol.

Modality	Tolerance [%]	PT		IMRT	
		Planned	Accumulated	Planned	Accumulated
Organs/Indices					
CTV7920	V79.2	96.9 ± 2.6	95.6 ± 3.8	99.5 ± 0.8	97.7 ± 2.6
	V77.6	100.0 ± 0.0	99.7 ± 0.9	100.0 ± 0.0	99.9 ± 0.1
CTV5040	V50.4	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
PTV7920	V77.6	98.6 ± 2.1	95.9 ± 5.0	98.1 ± 0.6	94.2 ± 3.3
PTV5040	V49.4	100.0 ± 0.0	100.0 ± 0.0	99.8 ± 0.8	99.8 ± 0.4
Bladder	V75	6.9 ± 3.1	6.0 ± 4.2	3.7 ± 2.4	3.9 ± 2.9
	V70	9.2 ± 4.4	8.7 ± 5.7	5.6 ± 3.6	6.1 ± 3.8
	V55	15.2 ± 6.9	16.0 ± 10.2	11.5 ± 6.6	13.1 ± 7.2
	V45	18.4 ± 8.2	21.0 ± 13.2	17.3 ± 9.5	19.4 ± 10.3
Rectum	V75	4.7 ± 1.2	4.0 ± 1.3	3.5 ± 1.2	3.8 ± 2.3
	V70	7.5 ± 1.6	6.6 ± 1.8	5.5 ± 1.6	5.9 ± 2.9
	V50	16.4 ± 3.7	15.9 ± 4.8	13.7 ± 3.7	14.4 ± 4.8
	V40	21.0 ± 5.3	21.0 ± 7.0	19.9 ± 5.8	20.8 ± 6.4
R femoral head	V45	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.5	0.1 ± 0.2
L femoral head	V45	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.3	0.1 ± 0.2