Impact Analysis of the Interobserver Variability in CBCT-Based Soft-Tissue Matching using TCP/NTCP Models for Prostate Cancer Radiotherapy

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Research

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Abstract

Background: Prostate alignment is subject to interobserver variability in cone-beam CT (CBCT)-based soft-tissue matching. This study aims to analyze the impact of interobserver variability in CBCT-based soft-tissue matching for prostate cancer radiotherapy.

Methods: Retrospective data, consisting of 156 CBCT images from twelve patients with intermediate- or high-risk prostate cancer were analyzed in this study. To simulate interobserver variability, couch shifts of 2 mm relative to the resulting patient position of prostate alignment were assumed as potential patient positions (27 possibilities). For each CBCT, the doses of the potential patient positions were recalculated using deformable image registration-based synthetic CT. The impact of the simulated interobserver variability was evaluated using tumor control probabilities (TCPs) and normal tissue complication probabilities (NTCPs).

Results: No significant differences in TCPs were found between prostate alignment and potential patient positions (0.944 ± 0.003 vs 0.945 ± 0.003, $P = 0.117$). The average NTCPs of the rectum ranged from 5.16 (%) to 7.29 (%) among the potential patient positions and were highly influenced by the couch shift in anterior-posterior direction. In contrast, the average NTCPs of the bladder ranged from 0.75 (%) to 1.12 (%) among the potential patient positions and were relatively negligible.

Conclusions: The NTCPs of the rectum, rather than the TCPs of the target, were highly influenced by the interobserver variability in CBCT-based soft-tissue matching. This study provides a theoretical explanation for daily CBCT-based image guidance and the prostate-rectum interface matching procedure.

Trial registration: Not applicable.

Background

As suggested by the National Comprehensive Cancer Network (NCCN) guidelines[1], the accuracy of prostate cancer radiotherapy should be verified by daily prostate alignment. The European Society for Radiotherapy and Oncology (ESTRO) guidelines recommended that prostate alignment must be based on either fiducial markers or CT-based soft-tissue matching[2]. Among these approaches, cone-beam CT (CBCT) is the most prevalent image guidance technique. However, CBCT-based soft-tissue matching is subject to interobserver variability, which is an obstacle in the standardization of prostate cancer image-guided radiotherapy (IGRT).

Several studies[3–8] have confirmed the interobserver variability in CBCT-based soft-tissue matching for prostate cancer radiotherapy. However, these previous studies primarily focused on analyzing the induced factors (e.g. observers' experience and image quality). To date, far too little attention has been given to the impact of interobserver variability in CBCT-based soft-tissue matching.

The purpose of this paper is to analyze the impact of interobserver variability in CBCT-based soft-tissue matching, thereby providing a theoretical explanation for the standardization of prostate cancer IGRT. To simulate interobserver variability, couch shifts of 2 mm relative to the resulting patient position of prostate alignment were assumed as potential patient positions. The dosimetric impact of the simulated interobserver variability on targets and organs as risk (OARs) was then evaluated using tumor control probabilities (TCPs) and normal tissue complication probabilities (NTCPs).

Methods

Patient data acquisition

In this study, retrospective data, consisting of 156 CBCT images from twelve patients with intermediate- or high-risk prostate cancer were analyzed. All patients received volumetric-modulated arc therapy (VMAT) with prescription doses of 76 Gy for the prostate gland and seminal vesicles (CTV1) and 60.8 Gy for the pelvic lymph nodes (CTV2) in 38 daily fractions. The clinical target volume (CTV) to planned target volume (PTV) margin is 5 mm in all directions. Notably, because the anatomical changes were similar between two consecutive fractions, the CBCT images were analyzed for every three fractions.

According to our clinical setting, the slice thickness of planning CT (SOMATOM Definition AS+, Siemens Medical Solutions, Forchheim, Germany) was 3 mm. Full-arc CBCT (On-board imaging v1.4, Varian Medical Systems, Palo Alto, CA, USA) was acquired on an Edge treatment system (Varian Medical Systems, Palo Alto, CA, USA) with a slice thickness of 2 mm. The patients were required to empty their rectum and bladder, drink 500 ml of water and provide feedback on the bladder filling state prior to CT localization and treatment delivery.

Dose reconstruction

Synthetic CT, generated by planning CT to CBCT deformable image registration in Velocity (v3.2.1, Varian Medical Systems, Palo Alto, CA), was used for interfractional dose calculation. Then, the CTV1, CTV2, rectum, and bladder were manually delineated on CBCT and mapped to synthetic CT. Finally, the origin plan is applied to the synthetic CT to calculate the interfractional dose in the Eclipse planning system (v13.6, Varian Medical Systems, Palo Alto, CA). To avoid interobserver variability in delineations, the targets and OARs on planning CT and CBCT were contoured by the same radiation oncologist.

Interobserver variability simulation

Prostate alignment visually aligns the prostate on planning CT and CBCT. In this study, prostate alignment was performed and recorded in the Mosaiq system by an experienced radiation therapist. To simulate interobserver variability, couch shifts of 2 mm relative to the resulting patient position of prostate alignment were assumed as potential patient positions. Consequently, a total of 27 potential patient positions were determined for each CBCT. Notably, we re-calculated the dose for every couch shift. The couch shifts relative to the resulting patient position of prostate alignment are listed in Table 1.

TCPs and NTCPs

The TCPs and NTCPs were calculated using the linear-quadratic Poisson model and the Lyman-Kutcher-Burman model, respectively. These calculations were performed using the open-sourced pyradiobiology package[9] and the physical dose exported from the Eclipse planning system. The radiobiology parameters and endpoints used for TCP and NTCP calculations were specified in previous studies[10–12].

Data analysis

The volumes of the rectum and bladder were calculated in the Eclipse planning system (v13.6, Varian Medical Systems, Palo Alto, CA). The impact of the simulated interobserver variability on the targets was evaluated using TCPs and the V_{95}, D_{98}, D_2, and mean doses of CTV1 and CTV2. The impact of the simulated interobserver variability on the OARs was evaluated using NTCPs and the V_{50}, V_{60}, and V_{70} of the rectum and bladder. Moreover, an independent sample t-test was performed to compare the resulting TCPs, one-way analysis of variance (ANOVA) were performed to compare the resulting NTCPs using the open-sourced statsmodels packages[13], and $P < 0.05$ was regarded as statistically significant.

Results

The rectal and bladder filling state

As shown in Supplementary Material A, the absolute and relative volume variations of the rectum and bladder were -4.9 ± 13.3/9.0 ± 61.0 ml and -6.1 ± 14.0/15.7 ± 31.4 (%), respectively. These results indicate that the patients were complying with the rectal emptying and bladder filling protocol.

The impact of the simulated interobserver variability on targets

Compared to the resulting dose parameters of prostate alignment, the absolute deviations of the V_{95}, D_{98}, D_2, and mean dose in CTV1 were 0.18 ± 0.37 (%), 0.82 ± 1.13 (%), 0.54 ± 0.54 (%), and 0.16 ± 0.13 (%), and those in CTV2 were 0.28 ± 0.52 (%), 0.67 ± 0.99 (%), 0.63 ± 0.66 (%), and 0.14 ± 0.22 (%) of the prescription doses for the potential patient positions, as shown in Fig. 1.

Figure 2 shows that no significant differences in TCPs were found between prostate alignment and the potential patient positions, which means that the simulated interobserver variability has a minor impact on the CTV1.

The impact of the simulated interobserver variability on OARs

As shown in Fig. 3, the volumetric dose parameters and NTCPs of the rectum were highly influenced by couch shifts in the anterior-posterior (AP) direction. On average, a 2-mm couch shift in the posterior

direction will contribute to 2.88 (%), 4.18 (%), 4.84 (%), and 0.97 (%) decreases in the V_{70}, V_{60}, V_{50}, and NTCPs of the rectum, respectively. The results of ANOVA indicate that the simulated interobserver variability has a statistical impact on the NTCPs of the rectum ($P < 0.001$).

In contrast, the volumetric dose parameters of the bladder were highly influenced by both the couch shifts in the AP and superior-inferior (SI) directions, as shown in Fig. 4. However, the average NTCPs of the bladder were within 1.12 (%) and relatively low. To an extent, the impact of the simulated interobserver variability on the NTCPs of the bladder is negligible.

Figure 5 shows an example of interobserver variability impact on dose volumetric histogram. In this treatment fraction, the decrease in the NTCP of the rectum was 1.16 (%), while the increase in the NTCP of the bladder was only 0.19 (%), using a 2-mm couch shift in the posterior direction.

Discussion

For the standardization of prostate cancer IGRT, it is more valuable to train observers to eliminate the interobserver variability in CBCT-based soft-tissue matching. Therefore, in this study, we attempted to analyze the impact of simulated interobserver variability on targets and critical OARs, thereby providing a theoretical explanation for the clinical practice of CBCT-based soft-tissue matching. Our analysis shows that only the NTCPs of the rectum were highly influenced by the simulated interobserver variability.

The TCPs of CTV1 were insensitive to simulated interobserver variability, which suggests the robustness of CBCT-based soft-tissue matching in terms of target localization. Surprisingly, this result is consistent with previous clinical trials. Napieralska et al.[14] reported that no significant differences in five-year progression-free survival were found between fiducial- and bone-based IGRT. As reported by Kotecha et al.[15] and Li et al.[16], CBCT-based soft-tissue matching is superior to fiducial-based IGRT in terms of target dosimetry, but a favorable rate of biochemical control was achievable using both IGRT techniques. This implies that a more accurate prostate target localization IGRT technique was not correlated with superior TCP.

Theoretically, various studies have demonstrated that a 3-mm PTV margin is sufficient[17,18]. Therefore, the CTV1 dosimetry would not be deteriorated by the 2-mm interobserver variability simulation because a 5-mm PTV margin was used in this study. Furthermore, several studies[19–21] have confirmed that PTV dosimetry is not sensitive to anatomical changes. Under this condition, the factors affecting the CTV1 dosimetry are interfractional deformation and intrafractional motion. Mayyas et al.[22] reported that prostate interfractional deformations were mainly due to rectal volume variation. Hence, the rectal emptying protocol was strictly carried out in our hospital. As a result, the absolute volume variations of the rectum were -4.9 ± 13.3 ml, negligibly small. In addition, Shelton et al.[23] verified that the intrafractional prostate motion was almost within 1 mm for the use of VMAT. This implies that a 5-mm PTV margin is sufficient to compensate for interfractional deformation, intrafractional motion, and simulated interobserver variability.

For CTV2, the ESTRO guidelines[2] recommended a 7-mm PTV margin, while a 5-mm PTV margin was used in this study. However, the changes in the CTV2 dosimetry induced by the simulated interobserver variability were similar to those in the CTV1 dosimetry (Fig. 1). A possible explanation for this is that the volumetric dose parameters in a larger target (CTV2) were less sensitive to the same couch shifts. In addition, pelvic lymph nodes were irradiated for prophylactic purposes. Therefore, the TCPs of CTV2 were not included in this study.

Interestingly, the NTCPs of the rectum were deemed to be highly influenced by the simulated interobserver variability, while the NTCPs of the bladder were not. This result may be explained by the fact that the average NTCPs of the bladder ranged from 0.75 (%) to 1.12 (%) among the potential patient positions. In other words, the changes in the NTCPs of the bladder were negligibly small. Moreover, this is consistent with the fact that the bladder is less radiosensitive than the rectum[11]. The volumetric dose parameters and NTCPs of the rectum were highly influenced by the couch shift in the AP direction, while those of the bladder were sensitive to the couch shifts in both the AP and SI directions (Supplementary Material B). This inconsistency may be due to the bladder being located in the direction superior to the high-dose PTV (PTV1).

Besides, Fiandra et al.[3] reported that the average interobserver variability between senior radiation oncologist and radiation therapist in LR, SI, and AP directions were 1.32 mm, 1.69 mm, and 2.05 mm, respectively. Similarity, the results in the study of Jereczek-Fossa et al.[6] were 1.9 mm, 0.9 mm, and -0.7 mm. Recently, Hirose et al. [5] took contour-based patient positioning as reference, and found that the average interobserver variations among six experienced radiation therapists in LR, SI, and AP directions were 0.5, 0.9, and 0.9 mm, respectively. Therefore, in this study, a maximum couch shift of 2 mm relative to the resulting patient position of prostate alignment were used for interobserver variability simulation. Furthermore, we simulated a maximum couch shift of 5 mm (with 1 mm stepwise) in anterior and posterior directions for one treatment fraction, and found highly linearity between the NTCPs of the rectum and couch shifts in anterior and posterior direction (Supplementary Material C).

The main drawback of this study is that the data from the prostate gland and the seminal vesicles were combined for analysis. As a result, the movements of the seminal vesicles independent of the prostate gland were not quantified. Therefore, in the process of CBCT-based soft-tissue matching, we ensured that the prostate gland and seminal vesicles were inside the prescription isodose line of the planned dose distribution.

Conclusions

In conclusion, the TCPs of the target can be effectively ensured by prostate alignment despite the interobserver variability in CBCT-based soft-tissue matching. The NTCPs of the rectum were deemed to be highly influenced by interobserver variability, while the NTCPs of the bladder were not. This provides a theoretical explanation for the prostate-rectum interface soft-tissue matching procedure[24]. More specifically, emphasis should be placed on both the rectum and the prostate in CBCT-based soft-tissue

matching. In addition, compared with fiducial-based target localization, volumetric CBCT-based soft-tissue matching is superior in utilizing anatomical information for the potential use of OAR sparing. For this reason, daily IGRT is superior to weekly IGRT in terms of OAR sparing. However, previous clinical trials[25–29] mainly focused on analyzing the IGRT-based PTV margin reduction for OARs sparing. Therefore, detailed investigations are needed to establish the clinical protocol for a specific IGRT technique[30].

Abbreviations

CBCT
Cone-beam CT
IGRT
Image-guided radiotherapy
OARs
Organ at risks
CTV
Clinical target volume
PTV
Planning target volume
TCP
Tumor control probability
NTCP
normal tissue complication probability
ANOVA
One-way analysis of variance
AP
Anterior-posterior
SI
Superior-inferior.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China School of Medicine, Sichuan University (No.20191128). All patients signed an informed consent form before radiotherapy.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xiangbin Zhang designed the study, collected data, analysis data, and drafted the manuscript. Xin Wang, Xiaoyu Li, Li Zhou, Shihong Nie, Changhu Li, Xuetao Wang, Guyu Dai, and Zhonghua Deng helped to collect the data. Renming Zhong designed the study, revised and final approved the manuscript. All authors read and confirmed the manuscript.

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Not applicable.

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Figures

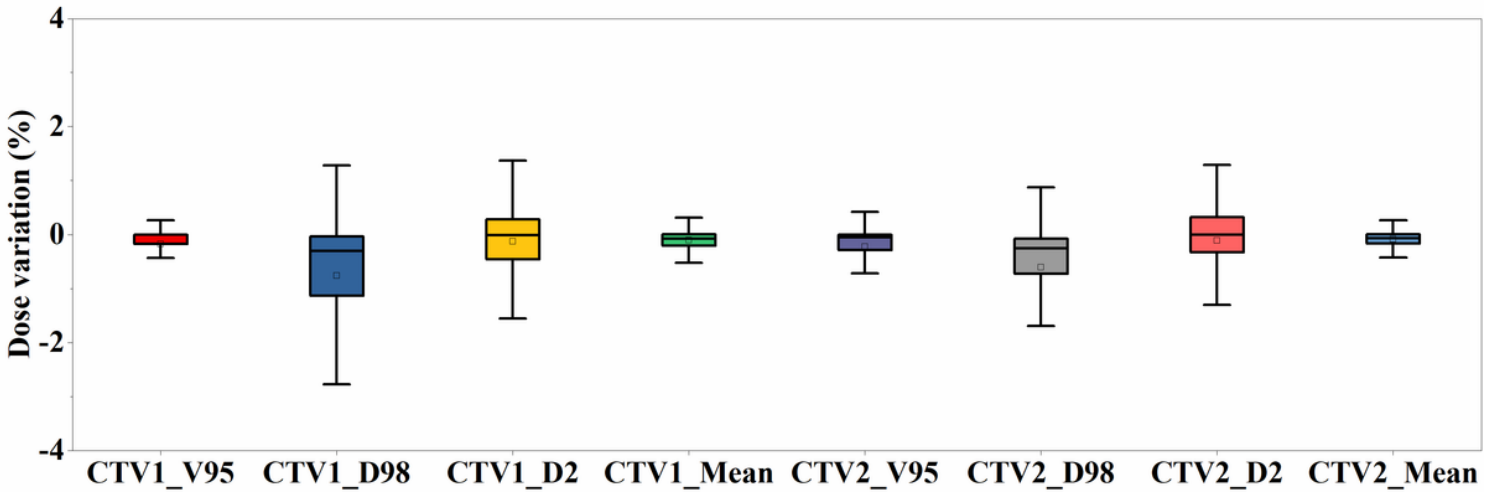

Figure 1

The changes in the target dosimetry induced by the simulated interobserver variability. Error bars represent standard deviation.

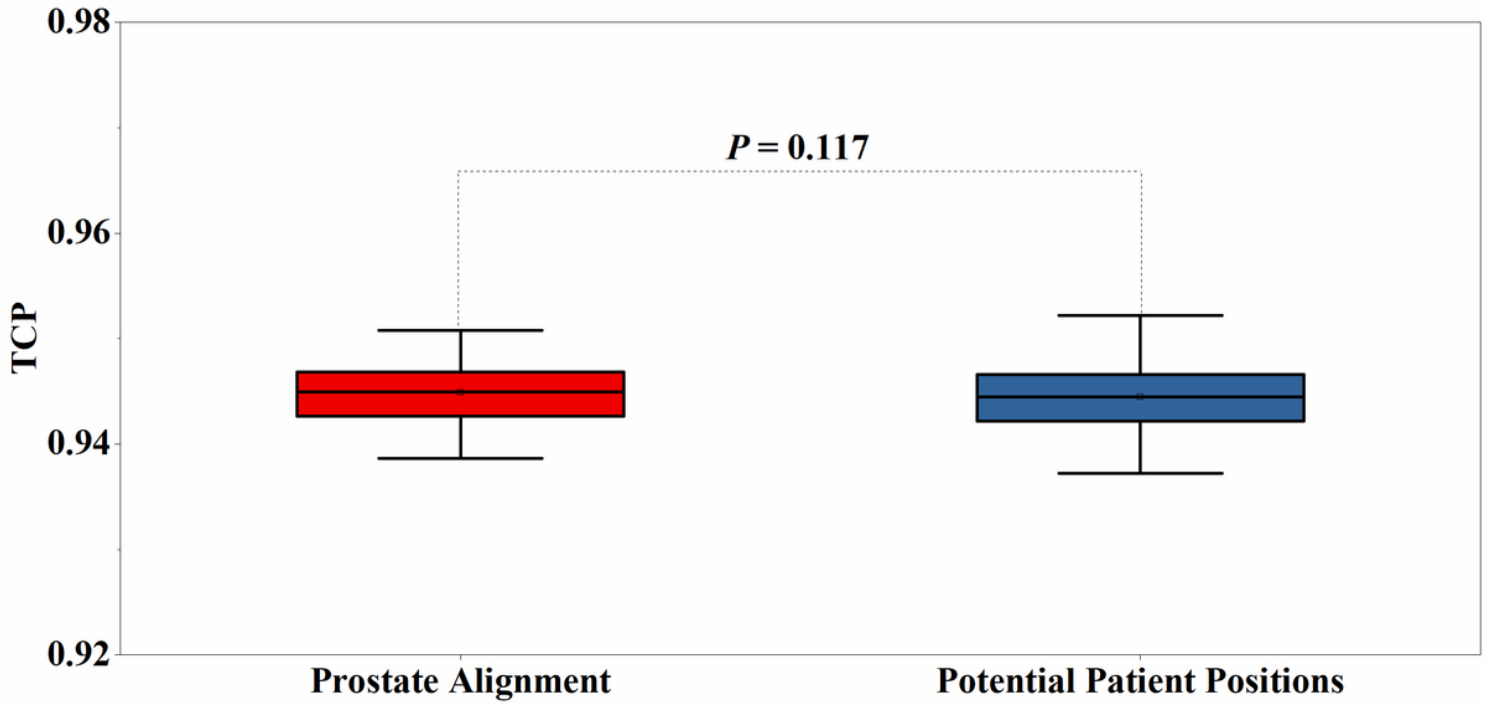

Figure 2

Comparison of the TCPs of CTV1 between prostate alignment and potential patient positions. Error bars represent standard deviation.

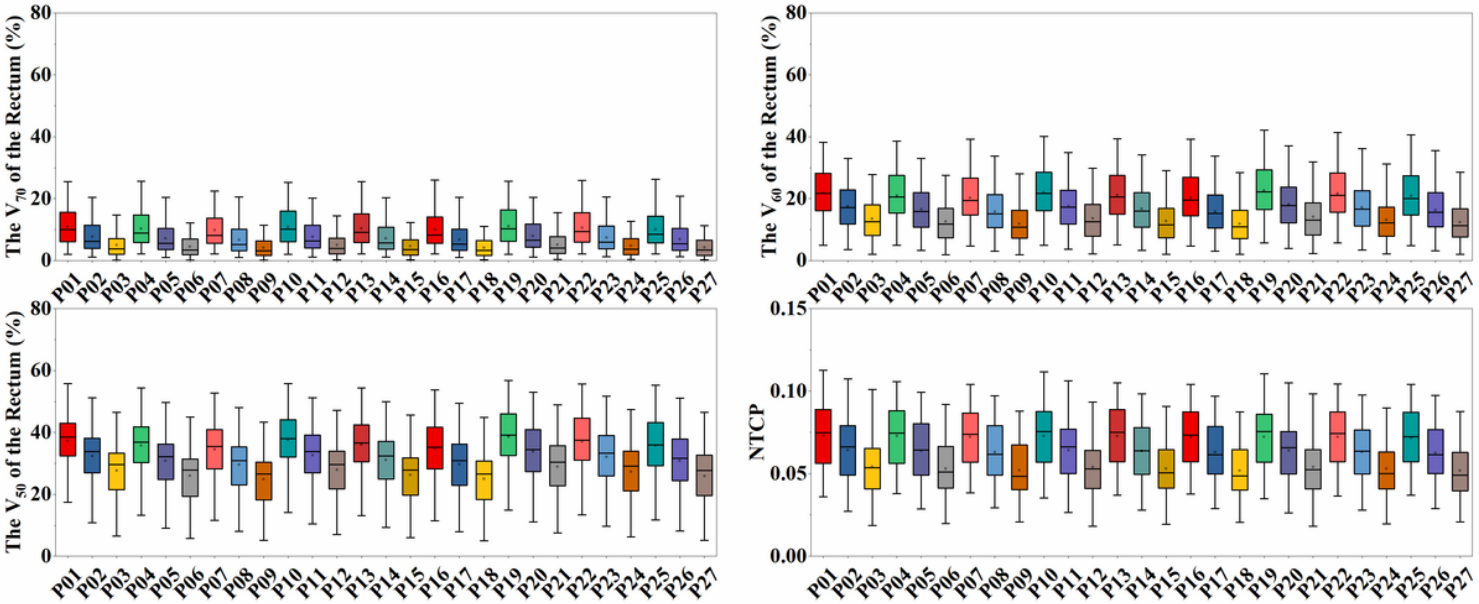

Figure 3

The volumetric dose parameters and NTCPs of the rectum among the potential patient positions. Error bars represent standard deviation.

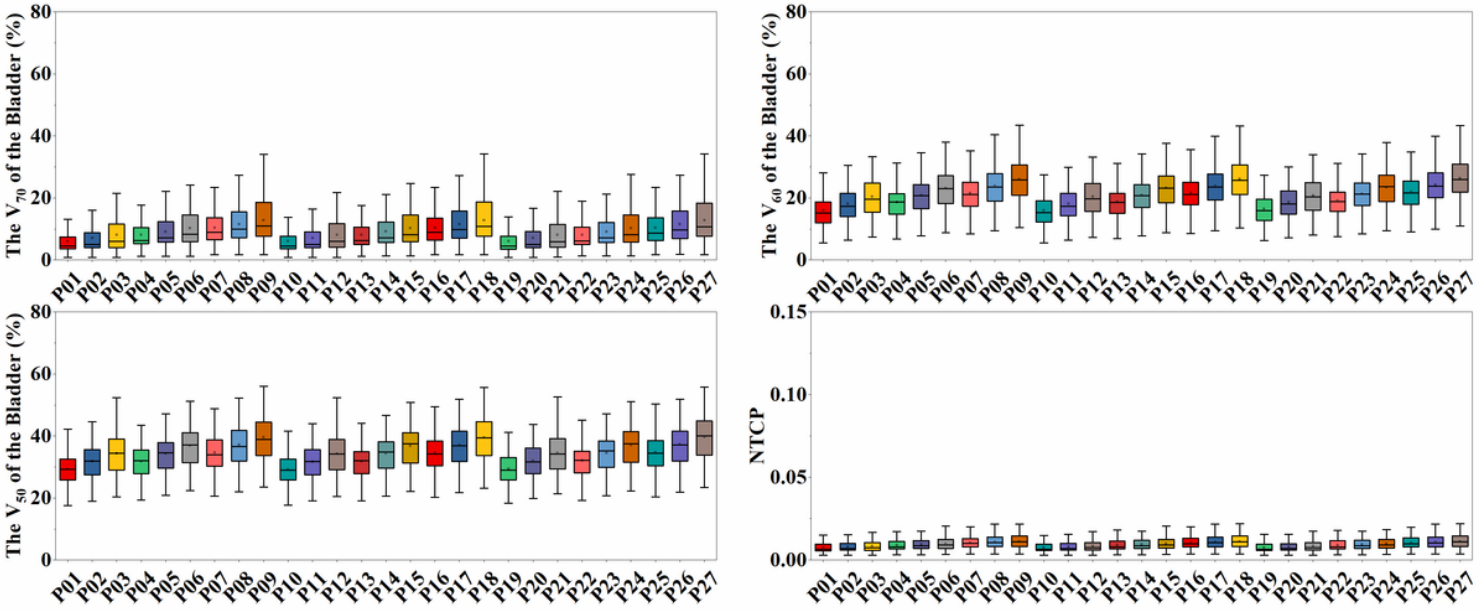

Figure 4

The volumetric dose parameters and NTCPs of the bladder among the potential patient positions. Error bars represent standard deviation.

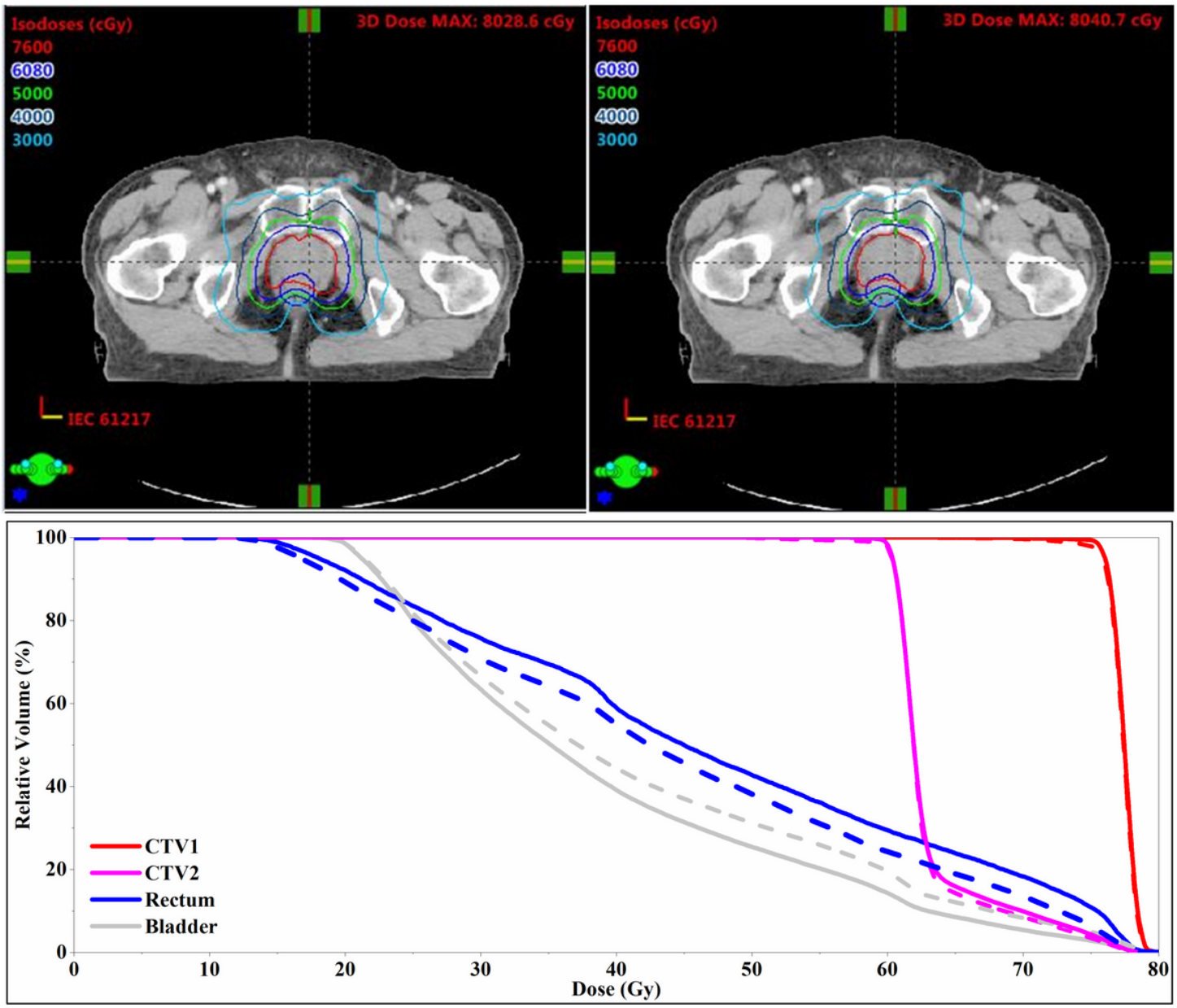

Figure 5

An example of interobserver variability impact on dose volumetric histogram. The solid dose volumetric histogram refers to prostate alignment and the dashed dose volumetric histogram refers to a 2-mm couch shift in the posterior direction.

Supplementary Files

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