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Interfraction Anatomical Variability Can Lead to Significantly Increased Rectal Dose for Patients Undergoing Stereotactic Body Radiotherapy for Prostate Cancer

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Abstract

Stereotactic body radiotherapy for prostate cancer is rapidly growing in popularity. Stereotactic body radiotherapy plans mimic those of high-dose rate brachytherapy, with tight margins and inhomogeneous dose distributions. The impact of interfraction anatomical changes on the dose received by organs at risk under these conditions has not been well documented. To estimate anatomical variation during stereotactic body radiotherapy, 10 patients were identified who received a prostate boost using robotic stereotactic body radiotherapy after completing 25 fractions of pelvic radiotherapy with daily megavoltage computed tomography. Rectal and bladder volumes were delineated on each megavoltage computed tomography, and the stereotactic body radiotherapy boost plan was registered to each megavoltage computed tomography image using a point-based rigid registration with 3 fiducial markers placed in the prostate. The volume of rectum and bladder receiving 75% of the prescription dose (V75%) was measured for each megavoltage computed tomography. The rectal V75% from the daily megavoltage computed tomographies was significantly greater than the planned V75% (median increase of 0.93 cm^3, $P < .001$), whereas the bladder V75% on megavoltage computed tomography was not significantly changed (median decrease of -0.12 cm^3, $P = .57$). Although daily prostate rotation was significantly correlated with bladder V75% (Spearman $\rho = .21$, $P = .023$), there was no association between rotation and rectal V75% or between prostate deformation and either rectal or bladder V75%. Planning organ-at-risk volume-based replanning techniques using either a 6-mm isotropic expansion of the plan rectal contour or a 1-cm expansion from the planning target volume in the superior and posterior directions demonstrated significantly improved rectal V75% on daily megavoltage computed tomographies compared to the original stereotactic body radiotherapy plan, without compromising plan quality. Thus, despite tight margins and full translational and rotational corrections provided by robotic stereotactic body radiotherapy, we find that interfraction anatomical variations can lead to a substantial increase in delivered rectal doses during prostate stereotactic body radiotherapy. A planning organ-at-risk volume-based approach to treatment planning may help mitigate the impact of daily organ motion and reduce the risk of rectal toxicity.

Keywords

SBRT, SABR, dosimetry, CyberKnife, IGRT

Abbreviations

AAPM, American Association of of Physicists in Medicine Task Group; CK, CyberKnife; CTV, Clinical Tumor Volume; HDR, high-dose rate; ICC, intraclass correlation coefficient; MRI, magnetic resonance imaging; MVCT, megavoltage computed tomography; OAR, organ at risk; PRV, planning organ-at-risk volume; PTV, planning target volume; RBE, rigid body error; SBRT, stereotactic body radiotherapy.

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Introduction

Stereotactic body radiotherapy (SBRT) for prostate cancer is rapidly growing in popularity. Several retrospective studies and phase 2 clinical trials have been performed evaluating SBRT for both definitive treatment for low-risk prostate cancer[1-8] and for prostate-specific boost in patients with intermediate and high-risk disease,[9-11] demonstrating promising biochemical-free survival results. Although these studies with follow-up out to 5 years generally report acceptable toxicity rates,[12] some have reported a relatively high rate of late urinary toxicity,[4] and 1 population-based study demonstrated a significantly higher rate of late urinary toxicity compared to conventional intensity-modulated radiotherapy.[13] In contrast, reported late rectal toxicity has been uniformly low, with the preponderance of evidence suggesting a rate of under 5%.[3-5,7,14]

Belying this low overall rate of toxicity is considerable uncertainty regarding dose constraints for normal tissues for prostate SBRT. AAPM TG101 has provided a set of constraints for pelvic organs, but these are based primarily on extrapolation from constraints from conventional fractionation and from empirical estimates by the authors of the report.[15] Many instead advocate using constraints derived from decades of clinical experience with prostate high-dose-rate (HDR) brachytherapy, which uses a similar dose and fractionation scheme to prostate SBRT and has been shown to yield dosimetrically similar treatment plans.[16-19]

To achieve conformal dose distributions comparable to HDR brachytherapy, robotic prostate SBRT combines sophisticated imaging and radiation delivery techniques. Specifically, fiducial markers implanted in the prostate are used to localize the prostate prior to treatment and track its motion throughout treatment delivery. This information is utilized by the robot to modify the radiation delivery to compensate for the changing prostate position. Several studies have been performed analyzing the intrafraction prostate motion during prostate SBRT.[20-25] These studies have all analyzed the time traces of the implanted fiducial markers and based on these data, planning margins and imaging frequency during treatment have been proposed. However, none of these studies have utilized volumetric imaging. Thus, anatomic changes that may occur either during treatment or between treatments, such as changes in rectal distension or bladder filling, were not investigated. Multiple studies have been performed investigating the impact of interfractional anatomical changes on the delivered dose distributions for more traditional, conventionally fractionated prostate treatments.[26-31] However, to the authors' knowledge, to date, this has not been investigated for SBRT treatments.

Stereotactic body radiotherapy planning and delivery for the prostate can be very different than for a conventional treatment protocol. For robotic SBRT, both translational and rotational corrections are utilized which, combined with continual tracking during treatment, has enabled very small planning target volume (PTV) margins to be used. The multiple noncoplanar angles utilized in robotic SBRT have also enabled very steep dose gradients and correspondingly inhomogeneous dose distributions. Thus, in contrast to conventional prostate radiotherapy, prostate SBRT may have much tighter PTV margins, steep dose gradients both inside and outside the prostate, and full translational and rotational position correction. The dosimetric effect of interfraction anatomical changes under these conditions is the focus of this study.

Methods

This study was approved by our committee on human research with a waiver of informed consent and was complaint with the Health Insurance Portability and Accountability Act.

To allow estimation of daily organ motion during prostate SBRT, 10 patients with intermediate or high-risk prostate cancer were identified. These patients had received a prostate boost using robotic SBRT with CyberKnife (Accuray Inc, Sunnyvale, California) to 19 Gy in 2 fractions, after completing a course of pelvic radiotherapy to 45 Gy in 25 fractions using helical tomotherapy (Accuray Inc). All patients underwent implantation of 3 fiducial markers within the prostate at least 1 week prior to computed tomography (CT) simulation. An initial CT scan (3-mm slice thickness) was acquired to plan the pelvic radiotherapy treatment. During treatment, patients underwent daily megavoltage computed tomography (MVCT) imaging during the pelvic radiotherapy portion of their treatment for daily alignment, with visualization of adjacent rectum and bladder. These MVCTs were used to estimate typical organ motion for the patient during prostate SBRT as described below, as volumetric imaging is not acquired prior to CyberKnife SBRT treatments.

For the SBRT portion of their treatment, a separate CT simulation with 1.5-mm slice thickness was acquired. For accurate prostate delineation, the CT was fused to a T2-weighted magnetic resonance imaging (MRI) sequence using point-based alignment to match the 3 fiducial locations. A T1 MRI sequence can also be used to guide the fiducial identification (fiducials provide a hypointense signal in the T2 sequence). Planning target volume was then generated by adding a 2-mm isotropic margin and by subtracting the rectum from the expanded prostate volume. All organs at risk (OARs; except the urethra, contoured on the T2 MRI sequence) were contoured on the planning CT. The whole bladder, from the base to the dome, was contoured. The rectum contour was defined from the anus to the rectosigmoid flexure.

Planning was performed using a sequential optimization method,[32,33] run to achieve the following goals: (1) to cover 95% of prostate PTV with 100% of the prescription dose, (2) to keep the volume of urethra (defined by MRI) receiving 120% of the prescription dose (V120%) under 0.1 cm^3, (3) to minimize the volume of rectum receiving 75% of the prescription dose (V75%), (4) to minimize the volume of bladder receiving 75% of the prescription dose (V75%), and (5) to ensure a conformal dose distribution, with no hot spots in normal tissue. As described previously, our planning method is based on empirical dose constraints

depending on individual patient anatomy.[33] In general, dose objectives of V75% <2 cm^3 and V75% <3 cm^3 were achieved for rectum and bladder, respectively, although relaxation of these constraints was allowed at the clinician's discretion. The prescription isodose line for the plans was in the range of 61% to 72%. During SBRT treatment, patients were generally instructed to empty their bowels and come with full bladder prior to each fraction. However, enemas were not routinely administered prior to daily treatment and rectal balloons were not used, per physician clinical practice at our institution based on low observed rectal toxicity following treatment. A low-fiber diet was encouraged for all patients.

For each patient, rectal and bladder contours were delineated on each of the 25 MVCTs obtained during pelvic external beam radiotherapy. Each MVCT image with accompanying rectal and bladder contours was then registered to the SBRT boost plan using a point-based rigid registration to the fiducial markers using proprietary software (MIM Software Inc, Cleveland, Ohio). Each registration was visually inspected to ensure correct fiducial alignment. The rectum and bladder contours drawn using the daily MVCT were transferred to the planning CT, and the volumes of each receiving at least 75% of the prescription dose (V75%) were found using the original planned dose distribution. For a subset of 10 MVCTs (1 for each patient), rectal and bladder contours were separately contoured by an independent investigator blinded to the original contours, and the intraclass correlation coefficient (ICC) between resultant V75% calculations was computed to assess for interobserver agreement.[34] The ICC is a standard way of measuring the consistency of measurements performed by multiple raters, with a P value <.05 indicating that we can reject the null hypothesis that the correlation between 2 sets of measurements occurred by chance.

To assess interfraction prostate rotation, the degree of prostate rotation in the sagittal plane (pitch) for each daily fraction was calculated using the positions of fiducial markers relative to the SBRT planning CT fiducial positions under the assumption of rigid body rotation.

Similarly, to assess interfraction prostate deformation, the distance between fiducial markers was first calculated based on fiducial positions on the SBRT planning CT:

$$D_{12}^{\mathrm{CT}} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + +(z_2 - z_1)^2},$$
$$D_{23}^{\mathrm{CT}} = \sqrt{(x_3 - x_2)^2 + (y_3 - y_2)^2 + +(z_3 - z_2)^2},$$
$$D_{13}^{\mathrm{CT}} = \sqrt{(x_3 - x_1)^2 + (y_3 - y_1)^2 + +(z_3 - z_1)^2},$$

where x_i, y_i, and z_i denote the coordinates of each fiducial marker i, and D_{ij}^{CT} denotes the distance between fiducials i and j.

For each MVCT image, distances between fiducials, D_{ij}^{MV} were then calculated according to the formulae above. The maximum rigid body error ($\mathrm{RBE_{max}}$) was calculated as the maximum difference in fiducial distance between SBRT planning CT and MVCT images:

$$\mathrm{RBE_{max}} = \max\left(|D_{12}^{\mathrm{MV}} - D_{12}^{\mathrm{CT}}|, |D_{23}^{\mathrm{MV}} - D_{23}^{\mathrm{CT}}|, |D_{13}^{\mathrm{MV}} - D_{13}^{\mathrm{CT}}|\right).$$

The degree of prostate pitch and prostate rigid body error was tested for correlation with the daily rectal and bladder V75%.

To investigate the methods of mitigating the impact of daily rectal and bladder motion on delivered OAR doses, separate SBRT plans for 2 patients were generated using various planning organ-at-risk volumes (PRVs). Three approaches were tried for generating the PRVs.

For the first method, rectal and bladder PRV contours for each patient were generated empirically from the union of all daily MVCT rectal and bladder contours for that patient and registered to the SBRT planning CT ($\mathrm{PRV_{empiric}}$). Contours were excluded from the PRV if the prostate pitch for that fraction exceeded 10° or if the rectum or bladder was not adequately visualized on MVCT. Using this technique, a unique, nonuniform PRV margin was obtained for the 2 patients. For the second method, the 6 patients not undergoing simulated replanning were analyzed, and it was determined that a 6-mm uniform expansion of the CK planning rectal contour covered at least 90% of daily MVCT rectal contours. This uniform expansion of 6 mm was then applied to the rectal contour from the CK planning CT for the 2 patients being replanned to generate a rectal PRV ($\mathrm{PRV_{expand}}$). For the third method, a planning structure was created by expanding the PTV by 1 cm in the posterior and superior directions and then excluding the original PTV to create an additional avoidance structure during treatment planning ($\mathrm{PRV_{shell}}$). The $\mathrm{PRV_{shell}}$ was constrained during optimization in addition to the typical objectives used for bladder and rectum. For all PRV-based planning techniques, plan characteristics and daily estimated rectal and bladder V75% were compared between the original SBRT plan and the PRV-based simulated plans.

Prior to analysis, the distributions of both bladder and rectum V75% as measured on daily MVCTs were tested for normality using the Shapiro-Wilk test[35]; both distributions differed significantly from normality ($P < .001$), so hypothesis testing was performed using nonparametric tests of group differences and correlations in subsequent analysis.

Results

Patient Characteristics

All 10 patients had localized, intermediate, or high-risk prostate cancer. Of the 10 patients examined, 8 rectums and 6 bladders were well visualized on MVCT on at least half of daily treatments, and analysis was restricted to these patients.

Rectal Dosimetry

An example of individual MVCT with registered SBRT boost plan is shown in Figure 1. For grouped statistical

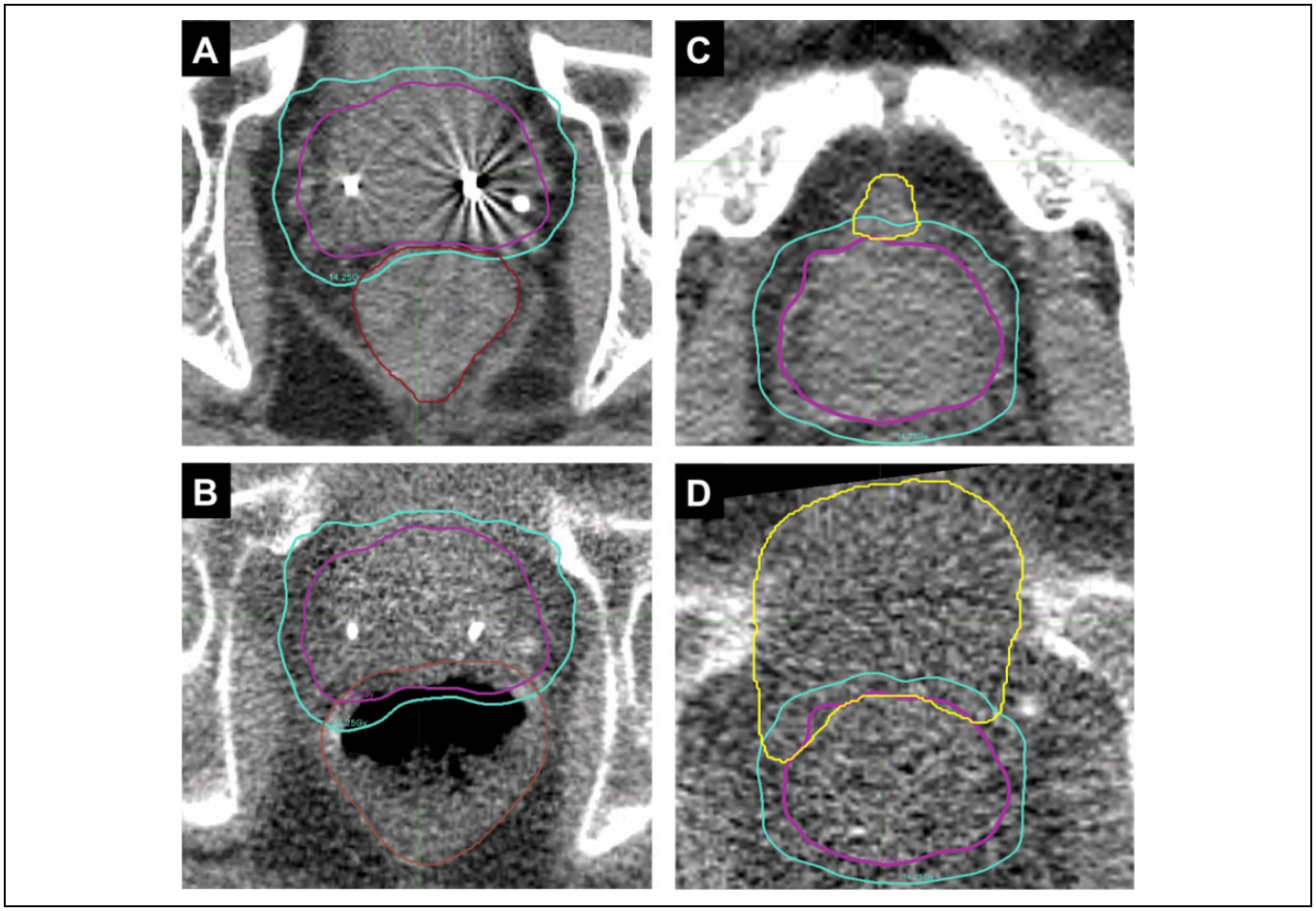

Figure 1. Rectal and bladder contours on planning computed tomographies and daily megavoltage computed tomographies (MVCTs). A, Rectal contour (brown) delineated on CK planning computed tomography (CT) for patient 5. B, Rectal contour delineated on an MVCT acquired during external beam radiotherapy, shown on same slice as (A). C, Bladder contour (yellow) delineated on CK planning CT for patient 1. D, Bladder contour delineated on MVCT acquired during external beam radiotherapy, shown on same slice as (C). For (A) to (D), prescription isodose line (19 Gy) is shown in purple, whereas the 75% isodose line (14.25 Gy) is shown in teal. Note: The color version of the figure is available at journals.sagepub.com/home/tct

analysis, the individual daily MVCT data for all 8 patients with adequately visualized rectums (173 total MVCTs) were combined. The rectal V75% increased by a median of 0.93 cm^3 (range: −1.5 to 14.0 cm^3) compared to the planned V75% (Figure 2A), which constituted a significant increase from plan V75% ($P < .001$ by 1-sample Wilcoxon rank sum test). For patients who met the initial dose constraints of V75% <2 cm^3 in the original SBRT boost plan (6 of the 8 patients), the daily rectal V75% exceeded this constraint on 47% of daily MVCTs. There was considerable individual variation in daily rectal motion, with subsequent variation in rectal dosimetry. Box plots of the change in the daily rectal V75% from the planned dose for each patient are shown in Figure 2B. One patient (#6) met rectal constraints of V75% <2 cm^3 on 75% of daily MVCTs, whereas another (#2) met this constraint on only 20% of daily treatments. There was good interobserver agreement for calculated V75% for a subset of 10 MVCTs contoured by a second investigator (ICC = 0.523, $P = .04$).

Bladder Dosimetry

For grouped statistical analysis, the individual daily MVCT data for 6 patients with adequately visualized bladders (114 total MVCTs) were combined. The bladder V75% changed by a median of −0.12 cm^3 (range: −4.93 to 5.46 cm^3) compared to the plan V75% (Figure 2C), which was not significantly different from the planned V75% ($P = .57$ by 1-sample Wilcoxon rank sum test). For patients who met dose constraints of V75% <3 cm^3 on the original SBRT boost plan (4 of the 6 patients), the daily bladder V75% exceeded this constraint on only 24% of daily MVCTs. In contrast to rectal motion, there was comparatively less individual variation in daily bladder motion, with less subsequent variation in bladder dosimetry. Box plots of the change in the daily bladder V75% from the planned dose for each patient are shown in Figure 2D. One patient (#7) met bladder constraints of V75% <3 cm^3 on 92% of daily MVCTs, whereas another (#1) met this constraint on only 68% of the MVCT images. There was excellent

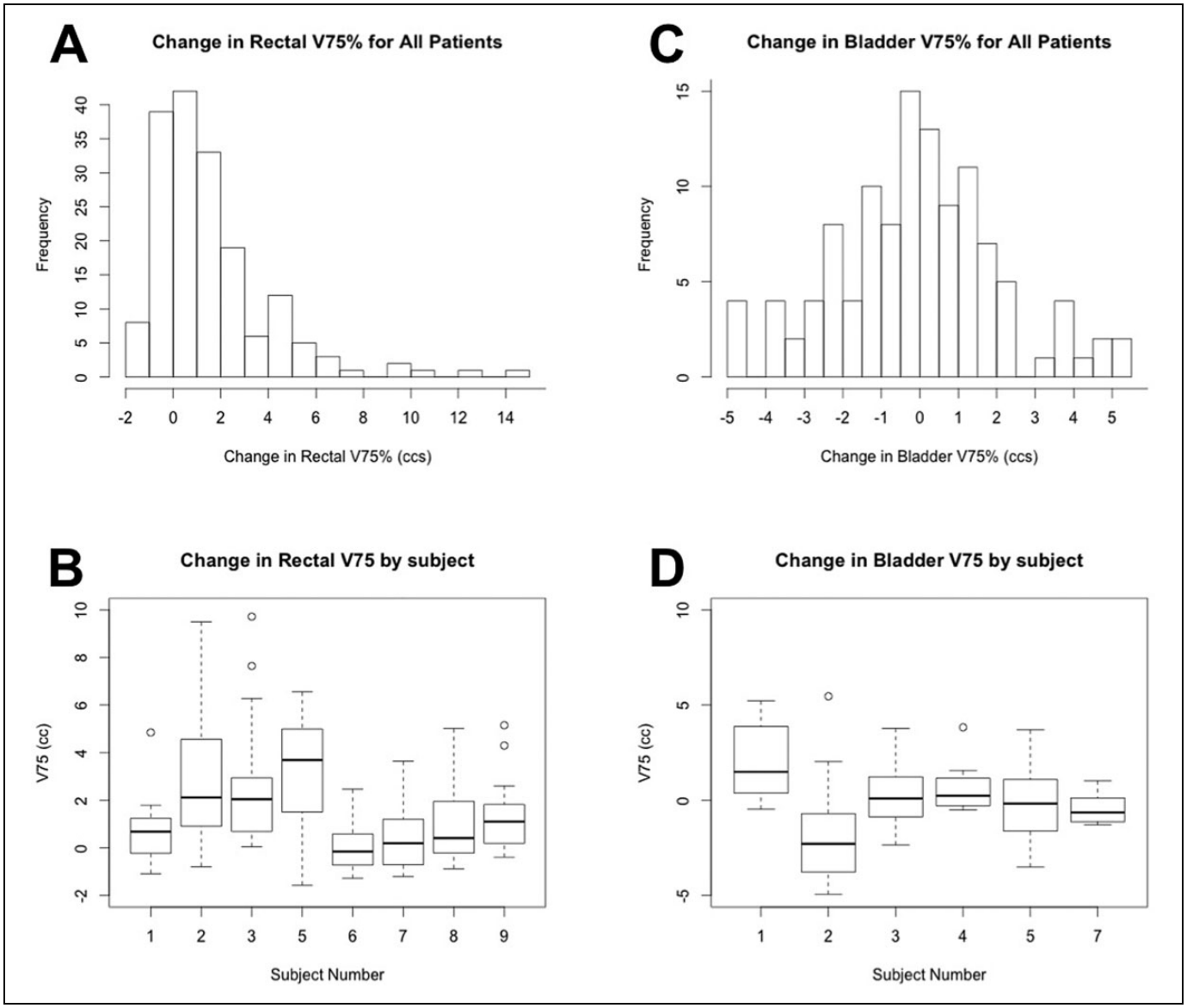

Figure 2. Rectal and bladder dosimetry. A, Distribution of changes in rectal V75% for all 8 patients analyzed. B, Distribution of changes in bladder V75% for all 6 patients analyzed. C, Boxplot depicting median and distribution of change in rectal V75% for each individual patient. D, Boxplot depicting median and distribution of change in bladder V75% for each individual patient. For boxplots, the lower and upper border of the box indicates the 25th and 75th percentile, respectively, the dashed whiskers indicate the 1.5 interquartile range above the upper quartile and the lower quartile, and the circles indicate outliers.

interobserver agreement for calculated V75% for a subset of 10 MVCTs contoured by a second investigator (ICC = 0.834, $P < .001$).

Relationship With Prostate Rotation and Deformation

To assess whether daily variation in rectal and bladder dosimetry could be predicted by prostate rotation, we recorded the degree of prostate pitch measured on each MVCT compared with the SBRT planning CT. The median magnitude of prostate pitch was 4.8° (range: 0.0°-28.6°). Although there was no significant correlation between the magnitude in prostate pitch and change in rectal V75% (Spearman $\rho = .075$, $P = .33$), we observe a weak but significant correlation between prostate pitch magnitude and change in bladder V75% (Spearman $\rho = .21$, $P = .023$). This analysis was also performed taking into account the direction of prostate pitch, with similar results. Using a threshold of 10°, the maximum amount of rotation that can be automatically compensated for using the CK machine, we find that MVCTs with a greater than 10° change in pitch do not demonstrate significantly greater rectal V75% compared with MVCTs with a less than 10° rotation (median V75% increase 1.19 vs 0.90 cm^3, $P = .2$ by Wilcoxon rank sum test). However, MVCTs with a greater than 10° change in pitch demonstrate significantly larger increase in bladder V75% compared with MVCTs with a less than 10° rotation (median

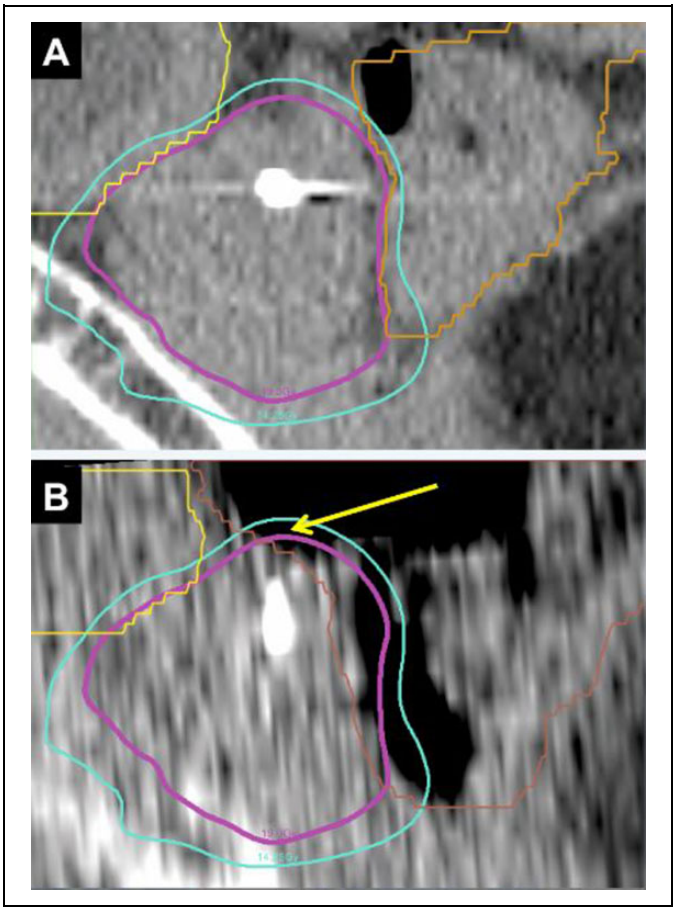

Figure 3. Example patient (#5) demonstrating variable rectal position and received dose without prostate rotation or deformation. Parasagittal view of the prostate, rectum, and bladder shown on (A) stereotactic body radiotherapy (SBRT) planning computed tomography (CT) and (B) daily megavoltage computed tomography (MVCT) during external beam radiotherapy. For both images, the rectal contour is shown in brown, the bladder contour is shown in yellow, the prescription isodose line (19 Gy) is shown in magenta, and the 75% isodose line (14.25 Gy) is shown in teal. The yellow arrow denotes a region of gas-filled rectum projecting superior to the prostate seen on MVCT, which yields a significant portion of the rectum receiving over 75% of prescription dose. This region was not contoured as part of the rectum on planning CT. For this MVCT, the prostate rotation (pitch) was 4.3°, maximum rigid body error (RBE_{max}) was 2.28 mm, and rectal and bladder V75% were 14.97 and 7.64 cm^3, respectively. Note: The color version of the figure is available at journals.sagepub.com/home/tct

V75% change +0.56 vs −0.27 cm^3, $P = .011$ by Wilcoxon rank sum test).

Similarly, the RBE_{max}, a measure of prostate deformation, was assessed for its ability to predict daily dosimetric changes. The median of the RBE_{max} across all patients was 1.45 mm (range: 0.09-5.52 mm). There were no significant associations between change in either rectal or bladder V75% and RBE_{max} ($P = .85$ and $P = .50$, respectively, by Spearman ρ). Figure 3 shows an example patient demonstrating a substantial increase in rectal V75% in the absence of significant prostate rotation or deformation.

Table 1. Treatment Plan Characteristics for Original SBRT Plan and 3 PRV-Based Replanning Techniques for 2 Example Patients.[a]

Plan Characteristic	Original	$PRV_{empiric}$	PRV_{expand}	PRV_{shell}
PTV coverage, %				
Patient 3	96.7	95.3	96.7	96.3
Patient 5	94.3	94.1	95.4	95.4
Urethra D_{max}, Gy				
Patient 3	20.8	21.2	21.4	21.3
Patient 5	22.3	22.4	22.2	22.0
Rectum V75%				
Patient 3	1.34	0.07	0.00	0.00
Patient 5	2.49	1.33	1.56	1.41
Bladder V75%				
Patient 3	2.39	2.84	2.42	2.37
Patient 5	3.94	4.04	3.63	5.81
Summed rectum V75%				
Patient 3	13.13	11.41	8.40	6.47
Patient 5	15.52	7.47	7.94	6.25
Summed bladder V75%				
Patient 3	5.14	5.88	5.24	4.81
Patient 5	4.99	3.84	3.72	6.06

Abbreviations: MVCT, megavoltage computed tomography; PRV, planning organ-at-risk volume; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

[a]Rectum and bladder V75% denotes the V75% as measured on the original SBRT rectal and bladder contours, respectively, while summed rectal and bladder V75% denotes the V75% as measured on a contour formed from the union of all daily MVCT rectal and bladder contours, with PTV subtracted from this union. All numbers are in units of cm^3.

Planning Organ-at-Risk Volume-Based Planning

For 2 patients demonstrating relatively large variations in daily rectal V75 (#3 and #5), we performed simulated planning using 3 PRV-based techniques: $PRV_{empiric}$, PRV_{expand}, and PRV_{shell}, as described in the Methods section. All 3 techniques maintained overall plan quality, while significantly decreasing the V75% received by both the original plan rectal contour and the union of all daily MVCT rectal contours, without significant alteration in bladder V75% (Table 1). Individual daily MVCT contours were also evaluated; the median change in daily rectal V75% was significantly reduced for all 3 techniques compared to the original CK plan (original plan median change: 2.4 cm^3, $PRV_{empiric}$: 0.08 cm^3, PRV_{expand}: −0.01 cm^3, and PRV_{shell}: 0.02 cm^3; $P < .001$ by Wilcoxon rank sum test for all 3 PRV-based techniques compared to the original plan). Figure 4 shows the dose–volume histograms for the original and PRV-based treatment plans, along with the distribution of rectal V75% on daily MVCT for each planning technique. Overall, the PRV-based planning techniques maintained similar PTV coverage, bladder V75%, and urethral D_{max} while improving daily rectal V75%, with a small decrease in the mean PTV dose.

Discussion

In this study, we used daily organ motion during conventional pelvic radiotherapy as a proxy for motion during prostate

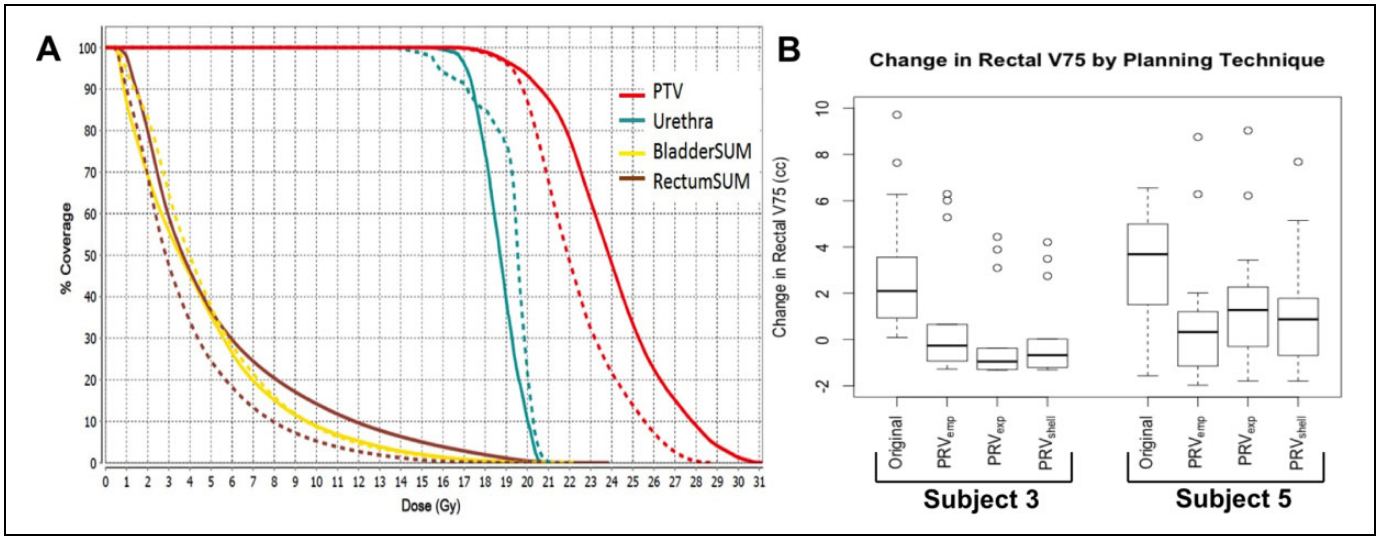

Figure 4. Planning organ-at-risk volume (PRV)-based planning technique with simulated replanning performed on patients 3 and 5. A, Dose–volume histogram (DVH) comparing original plan (solid) with PTV_{exp} plan (dashed) for planning target volume (PTV), urethra, sum of daily rectal contours (RectumSUM), and bladder contours (BladderSUM) for patient 3. B, Distribution of the change in daily rectal V75% using the original planning technique and 3 PRV-based planning techniques ($PRV_{empiric}$, PRV_{expand}, and PRV_{shell}). All PRV-based planning approaches significantly reduced daily rectal V75% compared to the original stereotactic body radiotherapy (SBRT) plan.

SBRT to investigate the effect of interfraction anatomical changes on the received OAR doses. To our knowledge, this is the first study investigating the effect of anatomical changes on prostate SBRT doses. A prior study examined the effect of intrafraction prostate motion on dose received by the prostate and the OARs,[21] assuming a fixed rigid relationship, but the lack of volumetric imaging has previously precluded examining the effect of deformations and other anatomical changes on rectum and bladder doses. For this reason, in this study, the patient's volumetric images acquired on another machine were used to define the representative motion for the patient.

Using these volumetric images as a proxy, we demonstrated that interfraction rectal organ motion can lead to significantly higher received rectal doses during prostate SBRT compared to the original SBRT plan dose. In contrast, the variability in bladder motion and received dose was more modest and not significantly different from the original SBRT plan dose. Some patients demonstrated highly variable rectal position with substantially higher corresponding rectal dose, whereas others demonstrated relatively reproducible rectal position. Based on this small case series, we cannot determine how frequently these large dosimetric deviations occur, but our observations do provide motivation to implement procedures to detect or mitigate the dosimetric impact of interfraction anatomical variation on prostate SBRT doses.

To this end, we examined whether metrics assessed at the time of daily SBRT treatment can be used to predict increased rectal and/or bladder doses as a result of organ motion. We found that there was a weak but significant correlation between prostate rotation in the sagittal plane (pitch) and received bladder dose, while no such correlation existed between rotation and rectal dose. Although the correlation between pitch and bladder dose suggests that the change in received dose was related to prostate rotational motion, this relationship was not sufficiently robust to be used as a clinical marker.

We also hypothesized that rectal distention or variable bladder filling may deform the prostate, and thus, measures of prostate deformation may be a marker for rectal or bladder dosimetric changes. However, rigid body error measurements for the implanted fiducials did not yield a significant association with received rectal or bladder dose. One possibility is that prostate deformation due to rectal distension or bladder filling is very localized to specific regions, and the 3 particular points marked by fiducials may not be sensitive to these changes. Alternatively, from a qualitative evaluation of the cases with large changes in OAR dosimetry, it appears that some of the increase in rectal or bladder dose is due to the OAR wrapping around the prostate in the MVCT without necessarily deforming it (Figure 3).

Prior work has shown that intrafraction prostate motion has minimal dosimetric effect on prostate CTV coverage and OAR doses, provided that the motion was detected and compensated for by robotic corrections during treatment.[21] However, that study was unable to assess the effect of nonrigid organ motion and subsequent changes to the dose due to the lack of volumetric imaging. Our study uniquely uses volumetric imaging to directly assess the effect of organ motion on OAR dosimetry. Crucially, we show that the dose to bladder and rectum may vary substantially even in the absence of significant prostate rotation or deformation when using fiducial markers as a surrogate (Figure 3). Thus, even perfect robotic corrections using fiducial marker tracking would not eliminate the dosimetric variability to surrounding OARs observed in our study.

Another option for managing the uncertainties from interfraction anatomical change is to create more robust treatment plans using PRVs during optimization. The PRV is an old concept that was developed prior to the advent of image-guided therapy and target tracking. Although there is a clear basis for reducing PTV margins with image guidance, there is no obvious relationship with PRV margins, and there have been very few studies investigating how PRV margins or definitions should be modified for image-guided therapy. One study of patients with prostate cancer imaged with cone-beam imaging found large variability in the daily rectal contours and was unable to define a population-based PRV margin that would be effective for planning conventional prostate radiation treatments.[36] In this study, we replanned a small subset of patients using multiple techniques aimed at accounting for daily rectal and bladder motion. Planning using any of these PRV-based techniques yielded substantially lower daily received rectal dose without compromising the overall plan quality. It should be noted that the replans based on these techniques maintained similar PTV coverage and doses to bladder and urethra, with a modest decrease in mean PTV dose, which to our knowledge has not been shown to be an important dosimetric determinate of outcome in prostate SBRT. Both a 6-mm isotropic expansion of the OARs in the treatment planning CT and an avoidance structure created by expanding the PTV 1 cm superiorly and posteriorly were found to yield significantly improved daily rectal doses. This standardized approach could be used clinically to account for daily rectal motion and potentially decrease risk of rectal toxicity without compromising the overall plan quality. Further analysis using this approach on a greater number of patients is required to better assess its clinical utility.

In addition to the need to account for daily organ motion during treatment planning, our findings suggest the importance of attempting to reduce daily organ motion through reproducible treatment setup. One potential limitation of our study is that we do not routinely use enemas prior to each treatment nor do we strictly verify compliance with a low-fiber diet. However, we are not aware of a definitive study demonstrating a benefit to implementing these interventions in this setting, and many published studies have not required daily enemas or rectal balloons.[2,4,7,14,37,38] However, some published prospective studies and the currently accruing multi-institutional phase 3 study for prostate SBRT, RTOG 0938, do require enemas prior to simulation and each daily treatment.[8,39,40] Our results demonstrate that variable rectal positioning during treatment can have a large dosimetric impact, supporting those efforts. It is unclear from our study the amount of rectal dosimetric variability that would be present for patients receiving daily enemas or rectal balloons; although these measures may mitigate the dosimetric effect of daily rectal motion, there may be significant additional organ motion not prevented by these measures. Further analysis of interfraction OAR motion with these measures in place would be required to determine whether significant interfraction OAR dosimetric variation occurs despite use of daily enemas.

Although our study suggests that daily organ motion increases the risk of elevated rectal doses during prostate SBRT, concerns over late side effects are generally related to late urinary toxicity, not to late rectal toxicity.[4,12,13] Our results suggest that the dose to the bladder neck is not greatly affected by interfraction prostate motion. However, interfraction or intrafraction motion may increase the risk of placing the intraprostatic urethra within a high-dose region (''hot spot'') for 1 or more treatments. The urethra was not well visualized on MVCT, and thus, the daily urethral motion was not evaluable in our study. The fact that reported late rectal toxicity is very low, despite our findings of significantly increased delivered dose to the rectum due to daily anatomic variability, can be accounted for by one of several possibilities. First, the true incidence of late rectal toxicity may be underreported in a body of literature consisting mainly of single-institution experiences and retrospective data. Second, currently accepted rectal dose constraints may be conservative and the true rectal tolerance for many patients greater than anticipated. Finally, interfraction rectal dose variability may be lower than that suggested by our study with a limited number of patients.

Some additional limitations of our study should be mentioned. First, soft tissue contrast in general was decreased in the MVCT images compared to the diagnostic kV CTs, so delineation of the OARs using daily imaging may not be as accurate as on planning CTs. However, contours by multiple observers demonstrated good interobserver agreement in measured OAR doses. Second, daily MVCT was used to define the daily OAR contour, but the 3-dimensional dose distribution for each day was assumed to be the same as the planned distribution. In reality, the change in patient anatomy and the change in beam arrangements due to target tracking will modify the delivered dose distribution. This change, however, is assumed to be a small effect on the OAR dose compared to the large modifications due to the change in relative position and distance of the OAR from the high-dose region. Third, per our institutional practice, 3 fiducials are used for prostate tracking during SBRT. Although some suggest that using 4 or more fiducials may minimize rotation measurement errors due to deformation or seed migration,[41] the use of 3 fiducials is common clinical practice and is allowed in the current multi-institutional trial, RTOG 0938. Furthermore, our observed deformations as measured by rigid body error were modest and did not correlate with the dosimetric data, suggesting that the addition of another fiducial may not significantly affect the rotation calculation or the dosimetric impact of the changing rectal geometry relative to the prostate. Finally, since volumetric imaging is not possible during robotic SBRT, volumetric images acquired on another machine were used a proxy to define the representative motion for the patient. For patients treated with SBRT on a conventional accelerator, cone-beam images acquired on the actual treatment day may be used to study this issue.

Conclusion

We demonstrate substantial interfraction variability in rectal position with resultant significant increases in daily rectal dose

during prostate SBRT. In contrast, bladder position was less variable, and daily bladder dose did not differ significantly from SBRT plan dose. Although bladder dose was weakly correlated with the degree of prostate rotation, measurements of prostate rotation and deformation using fiducial markers were not predictive of increased rectal or bladder doses in a clinically actionable way. Our findings highlight the importance of reproducible daily setup during prostate SBRT. In addition, a PRV-based approach to SBRT planning may help mitigate the dosimetric impact of daily motion on OAR dose. Although currently published results do not demonstrate a high rate of late rectal toxicity, longer follow-up from prospective studies is needed to better assess late toxicity and to further elucidate optimal dose constraints for patients undergoing prostate SBRT.

Declaration of Conflicting Interests

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