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Scientific Article

Daily Ultrasound Imaging for Patients Undergoing Postprostatectomy Radiation Therapy Predicts and Ensures Dosimetric Endpoints

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Abstract

Purpose: Patients who receive radiation therapy (RT) for prostate cancer are routinely positioned through radiographic means. We set out to establish a data-driven process that defines bladder volume required to meet V40/65 constraints using daily bladder ultrasound (US) and comparative cone beam CT (CBCT) before placing a patient on the treatment table.

Methods and Materials: This was a single institution retrospective study of 20 patients (390 CBCT scans) who received post-prostatectomy RT. Each patient received a daily US before treatment. CBCT alignment was performed 3 times a week. The bladder and rectum were contoured on each CBCT and a session dose was recorded. A mixed-effect model was used to estimate trajectory slopes of radiation exposure with organs-at-risk volume increase. Slope differences by V40/65 for prostate fossa (PF) and pelvic lymph nodes (PF/pLN) were tested using a 3-way-interaction term with Bonferroni correction.

Results: For the 20 patients, 10 received treatment to PF and 10 received RT to the PF/pLN. Predefined bladder constraints were V65 $<$ 50%, V40 $<$ 70%, and rectal constraints were V65 $<$ 35%, V40 $<$ 55%. The CBCT bladder volume (76-578 cm^3) was greater than the pretreatment bladder US (87-466 cm^3) due to volume filling between measurements ($r = 0.8 \pm 0.05$). Mixed model detected a statistically significant 3-way interaction ($P < .01$) for bladder volume and V40/65. Both PF and PF/pLN patients showed improvement in V40/65 with an increase in bladder volume. For PF patients, bladder constraints were met when the US volume was $>$108 cm^3 and for PF/pLN patients when the US bladder volume was $>$200 cm^3. Rectal filling showed no association with CBCT volume.

Conclusions: Daily US of the bladder before postprostatectomy RT allows for dosimetric predictions before daily treatment. This should translate into fewer CBCT for the patient and improved machine throughput. This technique is easy to institute and ensures organs-at-risk volumetric constraints are met based on daily US measurements.

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Introduction

Patients with prostate cancer generally adhere to a bladder filling protocol when undergoing radiation therapy (RT). This protocol is either based on treatment with a "comfortably full-bladder" or one that is centered around a voiding-filling-timing regimen to replicate the bladder filling at time of computed tomography (CT) simulation.[1-6] Treating patients with a full bladder is based on established dosimetric studies that demonstrate better sparing for the bladder and other organs at risk.[2,7-13] However, studies based on daily and weekly on-treatment imaging have shown that bladder filling varies and can result in dosimetric variances that differ from the initial CT scan (and planning dose volume histogram [DVH]).[12-14] These variations occur as patients progress through treatment because they have an increased frequency in urination and urgency or because it is challenging to practically coordinate the voiding-filling-timing regimen with busy machine schedules.[1,3] In either case, the variation introduces an uncertainty into the daily bladder volume that makes defining a true bladder dose constraint difficult because of the necessary adaptive imaging and dose deformation required.

Pretreatment and on-treatment bladder volumes have also been measured through a wide range of techniques.[1,4-6,15-18] Some of the most common regimens use daily or weekly cone beam computed tomography (CBCT) to compare the volumes with those at the time of simulation.[1,4,8,13,14,19] However, the bladder is a highly distensible organ and is unlikely to have a dose-volume represented by the planning DVH because of inconsistencies of the on-treatment bladder volume.[10] To reliably reproduce bladder filling so that the planning DVH represents dose actually seen by the bladder, an online adaptive strategy or pretreatment bladder protocol must be adopted.

Ultrasound (US) has been used to evaluate pretreatment bladder volumes.[5,6,16,17] The volume calculation has been shown to be an easy and reliable real-time method to obtain bladder volume with reasonable accuracy. Clinics have also used custom filling instructions and wait times based on US bladder filling rates to achieve a consistent and reproducible bladder volume.[3] Several groups have compared and validated daily US bladder volumes with pretreatment CBCT bladder volumes and found strong correlation in their results.[6,17]

Prior work related to daily US and CBCT imaging has focused on 2 separate components involved in patients' treatment: (1) daily/weekly CBCT to evaluate dosimetric bladder and rectum DVH values to report "true" endpoints based on daily anatomic variation and (2) the use of US to ensure a consistent and reproducible bladder volume. Our goal was to connect the 2 components, and to establish a data-driven process, via daily bladder US imaging and comparative CBCT, that defines bladder volume required to meet V40/65 constraints before placing a patient on the treatment table. Using the US-CBCT data, we extrapolated the bladder and rectum back to the planning CT using daily online registrations and calculated DVH values that corresponded with different bladder and rectum volumes. In this way, a daily US technique can easily be applied to evaluate a patient's organs-at-risk (OAR) dosimetry while reducing the need for daily CBCT or adaptive planning. The method established here addresses a problem that is increasingly important as clinics are experiencing a greater number of postprostatectomy RT (PPRT) patients. In the last 4 years, the number of PPRT patients we have consulted has grown by more than 75%, from 156 patients in 2016 to 276 patients in 2019. Our technique and protocol help reduce the number of CBCTs that would be performed while also reducing the patient's time on the treatment table.

Methods and Materials

Patients

This retrospective single-institution study was approved by the institutional review board. Twenty patients were chosen who received PPRT between January and December at Norris Comprehensive Cancer Center (Los Angeles, CA) in 2019. The patients were randomly selected from those treated on our Varian Truebeam STX machine because of its CBCT image quality. Ten patients underwent treatment to the prostate fossa (PF) and 10 patients received treatment to the prostate fossa and pelvic lymph nodes (PF/pLN).

Simulation

Patients were instructed to have an empty rectum (attempt bowel movement) and comfortably full bladder by drinking approximately 1 L of water 30 minutes before CT simulation. Therapists were instructed to verify the volume using a Hitachi Aloka US to ensure filling was >100 cm^3 before proceeding with CT simulation. Volume measurements were performed using a 3-axis prolate ellipsoid method (Fig 1). All therapists underwent the same US training and used the same measurement technique. Patients were simulated head-first supine with arms on their chest and legs immobilized in a CIVCO combi fix baseplate system. No patients considered in this study used space OAR or had implanted fiducials.

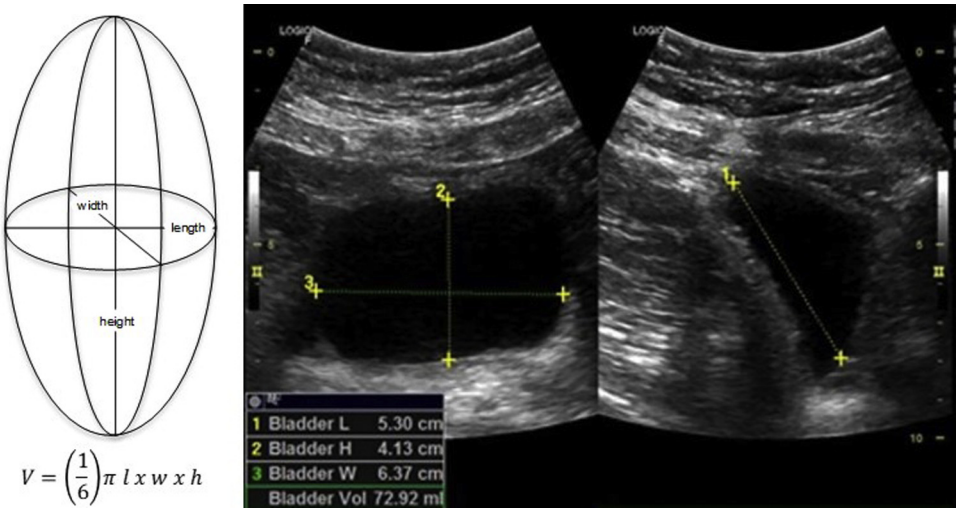

Figure 1 Prolate ellipsoid method of acquiring bladder volume via ultrasound.

Dosimetry

Prescription dose to the prostate bed was given at 200 cGy per fraction and ranged from 6600 to 7000 cGy with 4600 cGy to the lymph nodes when included. All patient treatment plans used volumetric-modulated arc therapy with 6 MV photons. Target coverage constraints were 95% of the planning target volume > prescription dose with constraints of V65 < 50%, V40 < 70% for the bladder and constraints of V65 < 35%, V40 < 55% for the rectum.

Treatment

Before being placed on the treatment table, each patient received a daily US to confirm a bladder volume within ±20% of the volume recorded at CT simulation. If the US volume was not within this range, then the patient was instructed to drink more water and rechecked 15 minutes later. Three times a week, CBCT verification was performed. The therapy team was instructed to review the clinical target volume (CTV), rectum, and bladder contours during CBCT. They were trained to ensure the CTV was skimming the pubic symphysis anteriorly, and the posterior CTV line abutted the anterior portion of the rectum. If this could not occur due to bladder or rectal filling, the attending was alerted to review and decide subsequent steps regarding alignment.

Analysis

Retrospectively, the bladder and rectum were contoured on each CBCT registered. Contours were transferred to the planning CT and a session dose was recorded corresponding to the "contours-of-the-day." A composite dose for all fractions was calculated using CBCT mean volumes. The bladder and rectum V65 and V40 composite dosimetric values were recorded. The ultrasound bladder volumes were compared against CBCT volumes. The values were stratified against 9 therapists who performed US. Daily CBCT shifts for patient setup were also stratified against the same 9 therapists.

Statistics

A mixed-effect model was used to estimate trajectory slopes of radiation exposure with OAR volume increase. Slope differences by V40/65 for PF and PF/pLN were tested using a 3-way-interaction term with Bonferroni correction for multiple comparison error.

Results

Ultrasound—CBCT

For the 20 patients considered, a total of 390 CBCT scans had corresponding US volumes. The CBCT bladder volume (76-578 cm^3) was greater than the pretreatment bladder US (87-466 cm^3), as shown in Figure 2, for more than 90% of the scans ($r = 0.8 \pm 0.05$). On average, the US volume underestimated bladder filling by 28.3% ± 14.3%.

Bladder V65/V40 for prostate fossa (PF)/pelvic lymph node patients (PF/pLN)

There were 194 PF and 196 PF/pLN CBCT scans that were contoured and registered with the planning CT. Contours were transferred to the planning CT and a session dose was recorded corresponding to the "contours-of-the-day." Two representative cases are shown in Figure 3a-d. The interfraction volumetric changes are

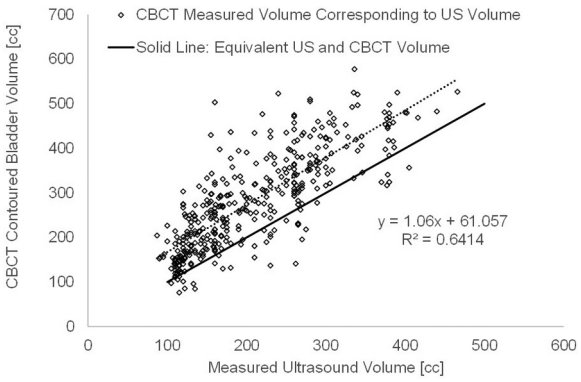

Figure 2 Bladder volumes compared with ultrasound (US) and cone beam computed tomography (CBCT). The solid line indicates a 1:1 comparison where the US volume directly coincides with the CBCT contoured volume.

illustrated by changes in the daily bladder contour while the corresponding DVH changes are also presented as indicated deviations from the baseline DVH.

The bladder V65 and V40 dosimetric endpoints are reported for all 390 CBCT scans in Figure 4a,b. Figure 4a provides the V65 values for increasing bladder volumes, and Figure 4b maps the corresponding US-CBCT data to the bladder V65 dosimetry. Similarly, Figure 5a provides the bladder V40 values for increasing CBCT volume while Figure 5b maps those CBCT volumes to the corresponding US. The dashed line indicates the volumetric planning constraint.

Rectum V65/V40 for prostate fossa (PF)/pelvic lymph node patients (PF/pLN)

The same analysis was performed for daily rectum contours, for example, rectum contours were transferred to the planning CBCT based on the therapist's online registration values and a DVH value obtained for V65 and V40 endpoints. Figure 6a and 6b provides the V65 and V40 values for the volumetric rectum dosimetry.

Mixed model detected a statistically significant 3-way interaction ($P < .01$) for bladder volume and V40/65; this same interaction was not observed for the rectum. Both PF and PF/pLN patients showed improvement in V40/65 with an increase in bladder volume, and PF patients had slightly improved results. For PF patients, bladder constraints were met when the US volume was >108 cm^3 and for PF/pLN patients when the US bladder volume was >200 cm^3. Rectal filling showed no association with CBCT volume.

Discussion

The primary objective of this study was to demonstrate that pretreatment daily US can predict cumulative

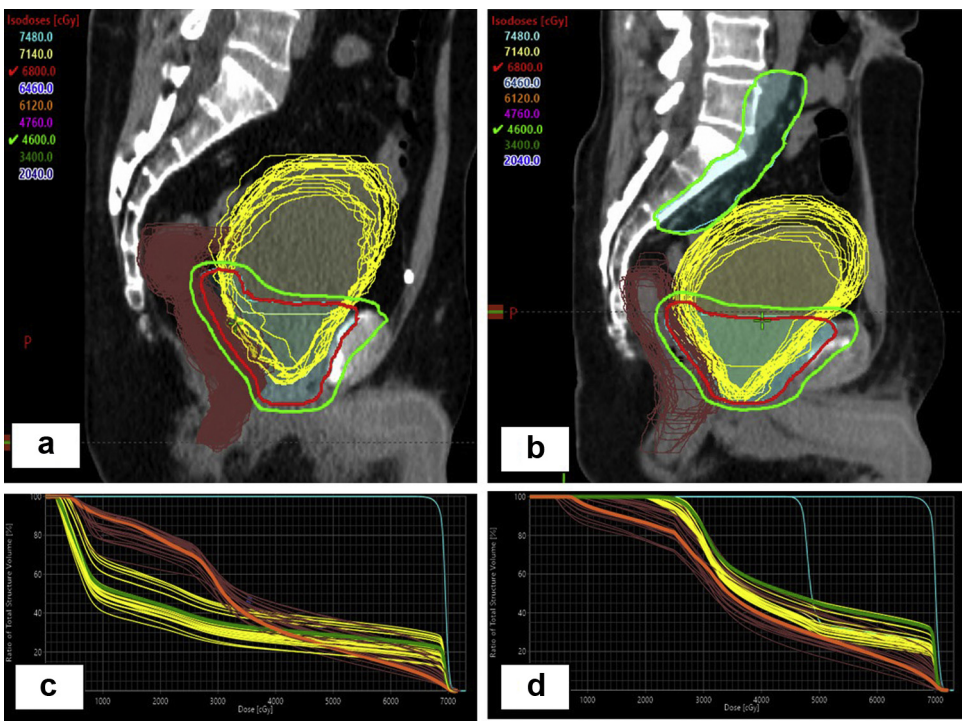

Figure 3 (a,b) Cone beam computed tomography (CBCT) contoured bladder and rectum volumes. Isodose lines, 4000 and 6800 cGy, are shown in green and red, respectively. (c,d) Corresponding dose volume histogram (DVH) curves when daily CBCT contours are evaluated against the planning computed tomography (CT). Solid orange line indicates planning DVH for the rectum, and solid green line indicates planning DVH for the bladder.

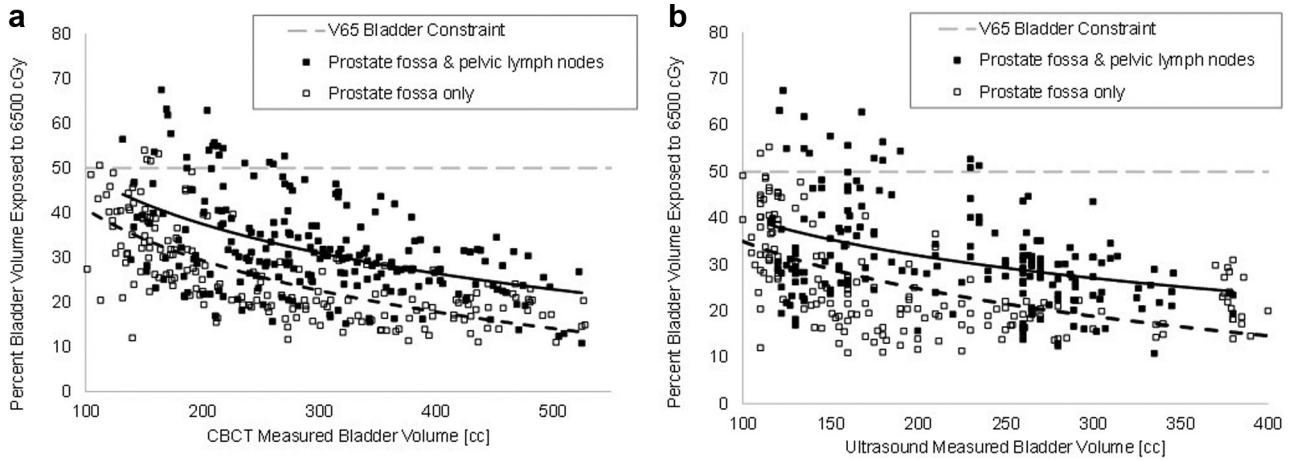

Figure 4 The dashed line indicates the bladder planning constraint V65 < 50%. (a) Bladder cone beam computed tomography (CBCT) V65 with solid square indicating prostate fossa (PF) and pelvic lymph nodes (PF/pLN) patients and white squares indicating PF patients only. (b) The corresponding ultrasound (US) bladder V65 values mapped from CBCT contours.

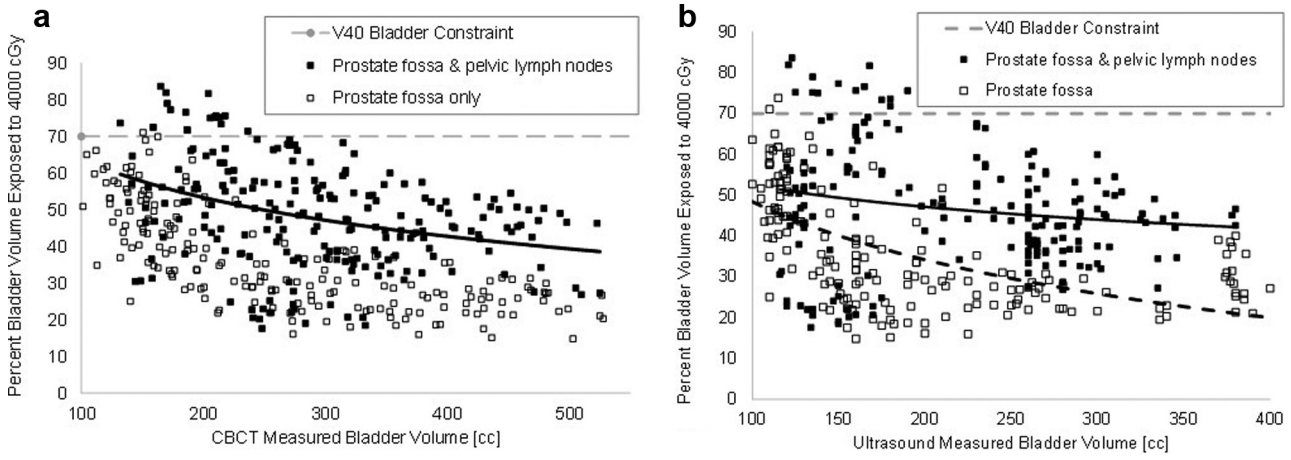

Figure 5 The dashed line indicates the bladder planning constraint V40 < 70%. (a) Bladder CBCT V40 with solid square indicating prostate fossa (PF) and pelvic lymph nodes (PF/pLN) patients and white squares indicating PF patients only. (b) The corresponding ultrasound (US) bladder V40 values mapped from cone beam computed tomography (CBCT) contours.

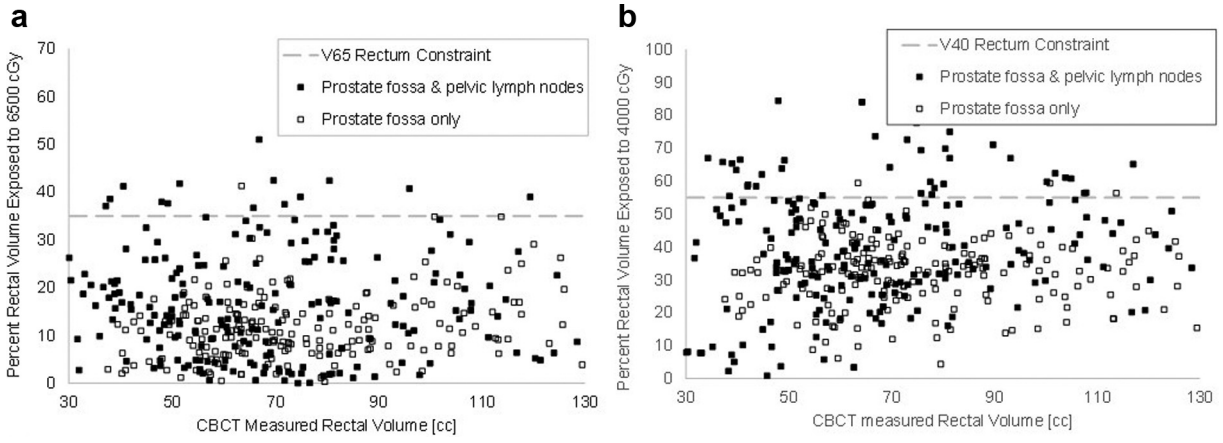

Figure 6 (a) Rectum cone beam computed tomography (CBCT) V65. The dashed line indicates the rectum planning constraint V65 < 35% with solid squares indicating prostate fossa (PF) and pelvic lymph nodes (PF/pLN) patients and white squares indicating PF patients only. (b) Rectum CBCT V40 with the dashed line indicating the V40 < 55% planning constraint.

dosimetry for patients with prostate cancer treated to the PF or PF/pLN. Daily radiographic image guided RT has been shown to improve biochemical progression-free outcomes for patients with prostate cancer.[14] Studies have reviewed the implications of radiographic imaging frequency (daily vs weekly) and the dosimetric consequences.[19] In fact, weekly imaging has been shown to be inadequate compared with daily imaging due to the daily changes in bladder volume and target positioning.[4,12] Because of this variability, it is unclear how accurately the DVH created based on CT simulation represents the actual dose to the bladder.[10]

To achieve consistent and reproducible bladder volumes, filling instructions and timing after voiding have been explored. Some studies have shown that a bladder US achieves more reproducible bladder filling during treatment of pelvic tumors.[17] However, patient instructions alone were not found to be sufficient in producing consistent and reproducible bladder filling, likely due to variability in patient adherence to instructions.[5] Analyses on optimal bladder filling have shown that it takes about 57 to 75 minutes after consumption of 500 cm^3 of water to achieve bladder filling measured at 180 cm^3.[3,6] These studies, however, did not analyze the effect of bladder filling variability on dosimetry.

Consistent with other studies, we had strong correlation between US and CBCT ($r = 0.8 \pm 0.05$).[17] The second part of our analysis focused on using the daily CBCT contours and translating those into a bladder "dose-of-the-day." Our data show patient daily bladder US values translate into bladder CBCT volumes that routinely exceed their values at time of CT simulation. This is contrary to prior data with fewer time points that showed CT simulation overestimates both rectal and bladder filling.[8] Our data highlight and emphasize the use of daily US in generating accurate information on bladder volume. This is important because bladder filling can draw more or less of the organ into the high-dose region, resulting in a different dose distribution than represented on planning DVHs.

In general, as the bladder volume increases on US and CBCT, the bladder volume expands anteriorly-superiorly and away from the high-dose field. The effect for patients treated to the PF is more significant, as the nodal dose region surrounds more of the bladder volume in PF/pLN patients. Prior analysis determined that a minimum CBCT threshold of 150 cc was sufficient to meet bladder dose-volume constraints for 90% of patients. The authors arrived at this value by creating a series of shrunken bladder volumes in 50 cm^3 increments.[11] The patient DVH data we present offer a more representative sample, with data granularity of approximately 1 cc. Both PF and PF/pLN patients showed improvement in both V40 and V65 with an increase in bladder volume. PF patients had improved results where $+10$ cm^3 increase in bladder volume translated to a -0.89% ($P < .01$) decrease in V65 compared with a -0.79% ($P < .01$) in V65 for PF/pLN patients. For example, a PF patient with a 200 cc bladder volume at the time of CT simulation is determined to have a bladder V65 = 40%. If this patient's average daily bladder volume was 300 cc, the resultant V65 would decrease to 31.1%. Similar dosimetric consequences are found when analyzing bladder V40 values. For a $+10$ cm^3 increase in bladder volume, PF patients experienced -1.11% ($P < .01$) in the bladder V40, whereas PF/pLN patients had a -0.75% ($P < .01$) in V40 values. For PF patients, bladder constraints were met when the US volume was >108 cm^3 and for PF/pLN patients when the US bladder volume was >200 cm^3. Rectal filling showed no association with CBCT volume. Results from Figure 6a,b demonstrate that rectum constraints are insensitive to PF or PF/pLN patients or volumes.

Limitations of this study include US user bias and variability between our 9 therapists. Additionally, the precise reporting of time from US to radiation treatment was not logged. As a retrospective study, these limitations are expected and help explain some data variance we report in both US volumes and the delta in volumes from time of US measurement to the corresponding CBCT reported volume.

Conclusions

Daily US of the bladder before postprostatectomy RT allows for dosimetric predictions before daily treatment. This should translate into fewer CBCT for the patient and improved throughput on the machine. This technique is easy to institute in routine clinical practice and ensures OAR volumetric constraints are met based on daily US measurements.

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