

## Original Article

# Quantifying daily variation in volume and dose to the prostate, rectum and bladder using cone-beam computerised tomography

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## Abstract

**Introduction:** In the era of dose escalation for localised prostate cancer, the dose–volume histogram (DVH) is integral to the assessment of rectum and bladder dose constraints. However, reliance on a single planning computerised tomography-based (P-CT) dose distribution may not account for variations in delivered dose that results from deformation of the prostate, bladder and rectum. This study uses cone-beam CT (CBCT) datasets from five patients to investigate the concordance between the dose prediction from the initial treatment plan and the dose delivered during treatment.

**Methods:** The intensity-modulated radiation therapy distribution used for treatment was superimposed on alternate day CBCT images for each patient. Dose metrics and absolute volumes for the prostate, rectum and bladder were extracted from the CBCT-based DVH. Differences in dose and volumes were compared with the P-CT values, and significance was tested using the Wilcoxon signed-rank test.

**Results:** For all five case studies, the prostate dose coverage on CBCT plans was lower than predicted with an average reduction of 3% in mean dose. Significant differences in rectal volumes and dose were observed in two out of five and four out of five patients, respectively. Reductions in bladder volume and subsequent increases in dose were observed for three out of five patients.

**Conclusion:** The DVH from P-CT was unable to consistently predict the dose delivered to the bladder and rectum. The current bowel and bladder preparation protocols used at our institution did not eliminate variation in bladder and rectum volumes for the five patients included in this study.

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**Keywords:** CBCT; DVH; IMRT plan; prostate cancer

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## INTRODUCTION

Intensity-modulated radiation therapy (IMRT) is a radiation therapy technique that enhances

the therapeutic ratio by producing a highly conformal dose distribution around a tumour target while sparing sensitive surrounding structures. In the treatment of localised prostate cancer, IMRT has facilitated dose escalation resulting in improved disease control without compromising acceptable long-term morbidity.<sup>1</sup>

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With enhanced dose conformity and dose escalation, comes the equally important issue of addressing the inter-fractional movement of the prostate by using an appropriate image-guided radiation therapy (IGRT) strategy. Cone-beam computerised tomography (CBCT) is an IGRT technology that uses a kV source and a flat-panel X-ray detector to produce volumetric images of the prostate immediately before treatment delivery.<sup>2</sup> Therefore, CBCT allows correction of setup errors in addition to providing information on the shape and volume of the prostate, rectum and bladder.

An IMRT dose distribution optimises dose delivery by maximising dose surrounding the prostate clinical target volume (CTV), while constraining the dose delivered to surrounding organs such as the bladder, rectum and femoral heads. The relationship between late-rectal toxicity and high-rectal doses<sup>3,4</sup> has led to the derivation of dose volume constraints and the increased reliance on the dose–volume histogram (DVH) to evaluate a dose distribution.<sup>5</sup> Physiological changes can affect the size and shape of the bladder and rectum, which in turn can cause displacement and deformation of the prostate. Dosimetric studies indicate that variations in bladder and rectal volume do occur, and as a consequence, the initial single planning computerised tomography-based (P-CT) DVH may not be a reliable representation of delivered dose.<sup>6,7</sup>

Although there are recognised problems with using a CBCT dataset to compute dose calculations,<sup>8</sup> it is nevertheless suggested that the dosimetric results from CBCT-based plans are comparable with P-CT plans.<sup>9,10</sup> This study investigates the accuracy of the initial dose distribution in predicting the dose to the prostate, bladder and rectum for five patients treated with IMRT for localised prostate cancer. The hypothesis tested is whether the treatment dose to the rectum and bladder calculated from CBCT datasets is significantly different from the dose predicted by the initial P-CT plan. This study reports on the variations in bladder and rectum volumes from CBCT compared with the P-CT volumes and also provides data on the efficacy of the rectal and bladder preparation currently used at our institution.

## MATERIALS AND METHODS

### Patient group

The study cohort consisted of five patients diagnosed with localised adenocarcinoma of the prostate treated with a five-field IMRT technique with daily CBCT imaging as part of routine care. The study was retrospective and consisted of consecutive patients who had no record of a transurethral resection of the prostate defect. All patients received bladder and bowel preparation instructions using a standard protocol and these instructions were reinforced on a regular basis by the radiation therapist (RT). The patient is instructed to take two tablespoons of Milk of Magnesia the night before CT Simulation and before each treatment and must ensure that they have a bowel movement. Full bladder instructions consist of asking the patient to empty their bladder and drink 500 mL of water 1 hour before CT simulation and before each treatment. The University of British Columbia-BCCA research ethics board approved the study.

### CT simulation and planning

Planning CT images were acquired using a GE Discovery CT scanner (GE Medical System, Milwaukee, WI, USA). The patients were scanned in the supine position with a knee wedge and ankle stocks. CT slices were acquired from the top of the iliac crest to 5 cm below the ischium using 2.5 mm slice thickness. All patients were planned using a five-field IMRT technique with 6 MV photons. The dose prescription was 74 Gy in 37 fractions and plan optimisation ensured that 98% of this prescription was delivered to 98% of the prostate CTV. The planning target volume (PTV) consisted of a 10 mm margin in all directions around the CTV, except posteriorly where a 7 mm margin was used. The plan ensured that 95% of the prescription dose was delivered to 99% of the PTV.

### CBCT acquisition

All patients were treated on a Varian Clinac iX Linear accelerator and initial setup was performed using simulation tattoos and alignment lasers. Daily online IGRT of the prostate was performed by the RTs using kV CBCT (Varian On-Board

Imager, version 1.5, Palo Alto, CA, USA). The CBCT image was acquired using 'pelvis' mode settings 125 kV, 80 mA, 13 ms and full scan with half-fan bow tie filter. The CBCT image was initially assessed using an automatic match algorithm and this match was further verified by the RT using a manual match tool. The CBCT was matched to the prostate and no threshold value was used during matching. All isocenter shifts were applied immediately before treatment so that the CBCT isocenter represented the treated isocenter. The post-imaging isocenter correction was therefore incorporated into the CBCT dataset that would be used during dose calculation.

### Contouring

Contouring of the CBCT and the planned CT simulation images was completed by two investigators using Varian Eclipse planning system (Varian, Palo Alto, CA, USA). The CBCTs from alternate treatment days were used so that 19 CBCT datasets were available for each patient. The use of day 1, 3, 37 CBCTs were considered representative of the entire treatment course and would capture any potential changes in rectum/bladder volume as treatment progressed.

A radiologist and a genitourinary radiation oncologist provided additional training to ensure consistency in the contouring process. The prostate CTV, rectum and bladder were outlined according to the Radiation Therapy Oncology Group contouring guidelines for the male pelvis. The prostate was contoured from the base to the apex, excluding the seminal vesicles. The bladder was contoured from the base to the dome and the rectum was contoured from the anus to the rectosigmoid flexure. The bladder and rectum were considered as solid organs during contouring.

In an effort to reduce inter-user variability in contouring, all CT and CBCT images belonging to an individual patient were contoured by the same investigator. The approved treatment plan distribution (i.e. the plan used to treat the patient) was copied and the original CT contours were deleted. The CT scan and all 19 CBCTs were then contoured during a single session in an effort to minimise variability in the

contouring procedure. Interpolation between contours was allowed and all contours were completed using the freehand and/or brush contouring tools.

### Dose calculation and DVH analysis

The field placements and fluence maps from the original (treated) plan were copied onto the P-CT and CBCT scans for each patient, and dose calculations were carried out using the Varian Eclipse analytical anisotropic algorithm. A dose grid increment of 2.5 mm was used. Consistent with recommendations in the literature,<sup>9</sup> the CT Hounsfield Unit (HU) number to electron density curve derived from a computerised imaging reference systems electron-density phantom was used for the CT and CBCT dose calculations.

Dose metrics and absolute volumes for the prostate CTV, rectum and bladder were extracted from the CT- and CBCT-based DVH. The raw data were exported from the Eclipse Treatment Planning System (TPS) and saved in an excel spreadsheet. An in-house MATLAB program was used to generate the cumulative DVHs using the files exported from the TPS.

The mean dose and the percentage of prescription dose delivered to 98% of the contoured CTV ( $D_{98}$ ) were recorded. The percentage volume of the rectum receiving >95%, 80% and 60% of the planned dose ( $V_{95 \text{ rectum}}$ ,  $V_{80 \text{ rectum}}$  and  $V_{60 \text{ rectum}}$ , respectively) and the percentage volume of the bladder receiving >95% and 68% of the planned dose ( $V_{95 \text{ bladder}}$ ,  $V_{68 \text{ bladder}}$ ) were recorded for all five patients. The percentage of CBCT plans that failed to meet the prostate IMRT constraints for rectum and bladder were also recorded. At our institution, the constraints for the rectum are:  $V_{95 \text{ rectum}}$  (<15%),  $V_{80 \text{ rectum}}$  (<35%) and  $V_{60 \text{ rectum}}$  (<50%). The constraints for the bladder are:  $V_{95 \text{ bladder}}$  (<25%) and  $V_{68 \text{ bladder}}$  (<50%).

### Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 14.0, Chicago, IL, USA). The Wilcoxon

signed-rank test was used to test the null hypothesis for the bladder and rectum. There was no significant difference ( $p = 0.05$ ) in the volume and dose recorded on the original plan compared with what was recorded at the time of treatment.

## RESULTS

### Prostate CTV

The mean (SD) percentage difference in the daily prostate CTV volume recorded on CBCT compared with the P-CT volume for patients A–E was:  $-4\%$  (9),  $+6\%$  (7),  $-6\%$  (5),  $+1\%$  (6) and  $-8\%$  (6), respectively.

For all patients, the mean CTV doses calculated on the CBCTs were lower than the mean dose recorded on the P-CT plan. The average difference (range) in mean CTV dose for patients A–E was:  $-2\%$  (0 to  $-4$ ),  $-3\%$  ( $-1$  to  $-5$ ),  $-4\%$  ( $-3$  to  $-6$ ),  $-3\%$  ( $-1$  to  $-4$ ) and  $-3\%$  ( $-1$  to  $-4$ ), respectively. Dose coverage was analysed with respect to the percentage of the prescription dose encompassing  $\geq 98\%$  of the contoured CTV volume ( $D_{98}$ ). Whereas all P-CT plans were within  $\pm 1\%$  of the planned IMRT dose constraints (i.e. 98% of prescribed dose to 98% of CTV), the CBCT-based plans consistently failed to reach these dose criteria (Figure 1). Patient A showed the least variation in dose coverage with a median  $D_{98}$  on CBCT of 95.5% compared with 97% calculated on the CT plan. Patients A, B and E had the best coverage to the CBCT CTV, with 16/19 (84%), 15/19 (79%) and 19/19 (100%) of the CBCT plans, respectively, encompassed by the 95% isodose value. Patient C had the worst dose coverage compared with the P-CT plan. On the basis of the CBCT plans, this patient achieved a median  $D_{98}$  of 93.6% versus 98.2% on P-CT plan and only 3/19 (16%) CBCT plans resulted in 95% isodose coverage to the CTV.

### Rectum

The median percentage difference between the CBCT and P-CT contoured rectal volumes for patients A–E was:  $+1\%$ ,  $-14\%$ ,  $-10\%$ ,  $+22\%$  and  $-29\%$ , respectively (Figure 2). Two patients

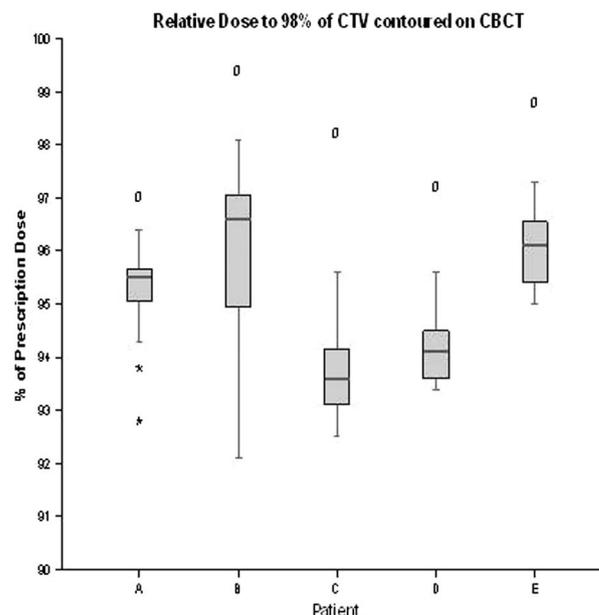


Figure 1. The relative dose to 98% of the prostate CTV ( $D_{98}$ ) as contoured on CBCT.

Notes: The original CT plan  $D_{98}$  is indicated by 0. The box plot displays median, lower and upper quartile range and outliers\*. Abbreviations: CTV, clinical target volume; CBCT, cone-beam computerised tomography; CT, computerised tomography.

(D and E) had rectal volumes that were statistically different ( $p < 0.001$ ) from the volumes on P-CT. Patient C had the most consistent rectal volume (range:  $+16\%$  to  $-24\%$ ), whereas Patient B recorded the largest variations in rectal volume (range:  $+36\%$  to  $-59\%$ ).

With the exception of patient A, the dose to the rectum tended to be less than the planned dose (Figure 3). Statistically significant differences between the planned and actual  $V_{95 \text{ rectum}}$ ,  $V_{80 \text{ rectum}}$  and  $V_{60 \text{ rectum}}$  were calculated for all patients, except for patient B. In the case of patient B, there was a significant difference in the  $V_{60 \text{ rectum}}$  value, but no significant difference in  $V_{95 \text{ rectum}}$  ( $p = 1.0$ ) or  $V_{80 \text{ rectum}}$  ( $p = 0.17$ ).

A CBCT plan was considered a failure if any one of the IMRT plan constraints for the rectum was breached. On the basis of this criterion, all patients passed with the exception of patient A and B, with failure rates of 12/19 (63%) and 3/19 (16%), respectively.

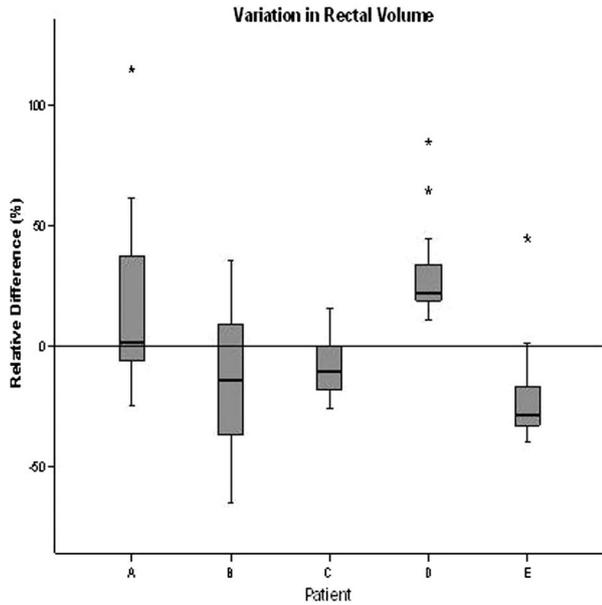


Figure 2. Variations in the volume of rectum contoured on CBCT compared with the original CT Plan contoured rectum.

Notes: The horizontal line represents the volume of rectum at CT. The box plot displays median, lower and upper quartile range and outliers\*.

Abbreviations: CBCT, cone-beam computerised tomography; CT, computerised tomography.

### Bladder

At the time of treatment, all the patients had a median bladder volume less than the volume on the P-CT (Figure 4). Although Patient A had the smallest bladder at CT (138 cc), this patient had the largest mean relative decrease in bladder volume recorded on CBCT (56.3%). Patients D and E had bladder volumes that decreased by an average of <5% of the CT volume and overall variations were not statistically significant for these two patients ( $p = 0.36$ ).

The mean dose to the bladder increased by an average of 56.3%, 55.8% and 31.4% for patients A, B and C, respectively. These three patients had statistically significant differences between P-CT and CBCT  $V_{68}$  bladder; however, the  $V_{95}$  bladder was significantly different only in the case of patient A.

Despite the relatively large increase in mean bladder dose, the plan fail rate based on IMRT bladder constraints for patients A, B and C was 3/19 (16%), 3/19 (16%) and 1/19 (5%),

respectively. Patients D and E showed good agreement with the P-CT plan, with an average difference in mean bladder dose <5%, no significant difference in  $V_{95}$  bladder or  $V_{68}$  bladder and 100% pass rate for the IMRT bladder constraints. A comparison of the bladder volume changes experienced by patients A and B offers further insight into the association between bladder volume and dose (Figure 5). Patient A had the smallest bladder volume at CT and this volume decreased further during treatment, with a correspondingly significant increase in bladder dose. This increase in dose can be explained by the caudal shift of a deflated bladder into the high-intensity dose of the PTV. In contrast, patient D had the largest volume at CT (338 cc) and this volume remained inflated, resulting in minor fluctuations in bladder dose.

### DISCUSSION

The decision to use CBCT datasets with direct application of the CT electron-density calibration curve was based on previous CBCT dose calculation-feasibility studies.<sup>9,10</sup> Although direct dosimetry for prostate cases is achievable using CBCT, dose errors of up to 3% are possible because of reduced image contrast, artefacts and patient size. In this study, the dose coverage to the CTV, as assessed by mean dose,  $D_{98}$ , and 95% isodose coverage were consistently lower at treatment compared with the planned dose. It is therefore plausible that the reduction in dose to the CTV can be explained by a systematic (but relatively minor) discrepancy between the CT and CBCT HU, resulting from the above-mentioned CBCT image reconstruction errors. On the assumption that an inherent dose underestimation of ~3% exists, an appropriate correction would result in all CTVs encompassed by the 95% isodose and four out of five patients would achieve a median  $D_{98} \geq$  the  $D_{98}$  recorded on the CT-based plan. If the above explanation of dose underestimation is accepted, then it would suggest that the use of our daily CBCT protocol, in combination with the PTV margin, results in consistent dose coverage of the prostate CTV.

As with other studies,<sup>7,11</sup> the results from this research indicate that large variations can occur

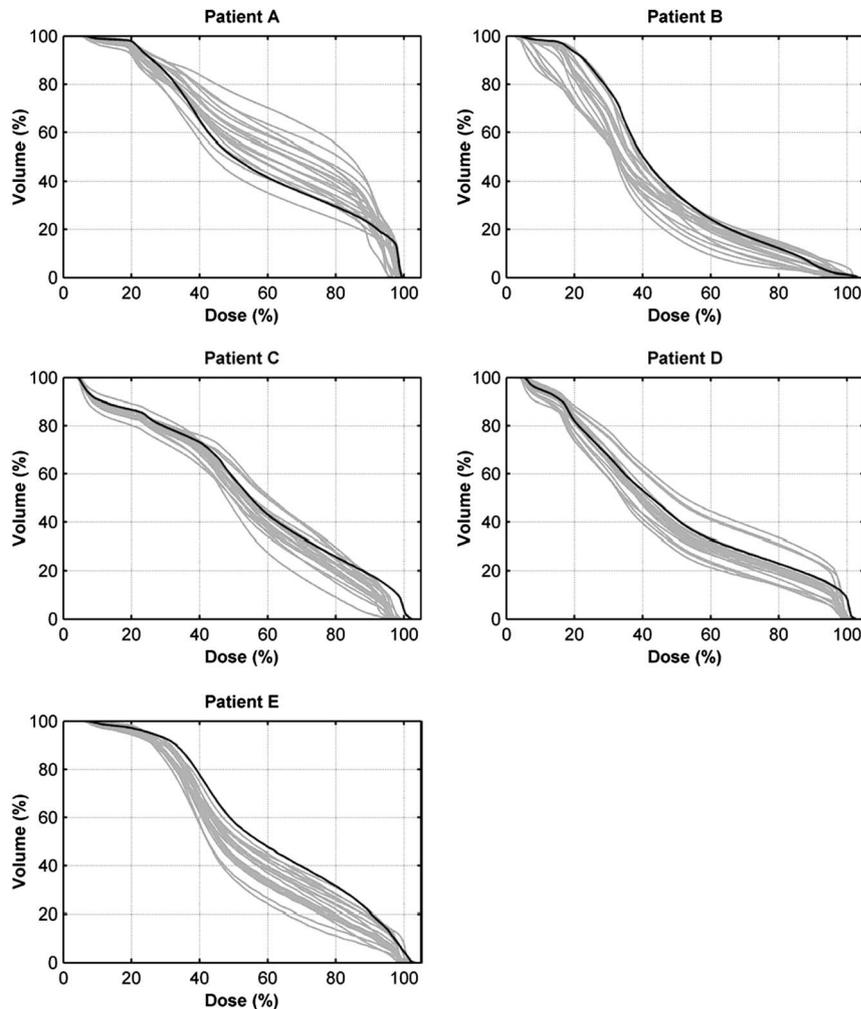


Figure 3. The rectum DVH for original CT Plan compared with the 19 CBCT-based plans for patients A–E.

Notes: The CT Plan is indicated in black and the CBCT plans are in grey.

Abbreviations: DVH, dose–volume histogram; CBCT, cone-beam computerised tomography; CT, computerised tomography.

between the rectal volume at CT and volumes at treatment delivery. These results also support the finding that some patients are able to maintain a more stable rectal volume than others.<sup>12</sup> Despite the use of a rectal preparation protocol and feedback from the RT on the perceived adequacy of the patients' level of rectal emptiness, a significant difference in rectal volume was observed for two out of five patients. During the CBCT contouring process, incidences of rectal gas and/or faeces were frequently observed in two patients, further questioning the efficacy of the present rectal preparation protocol. Although four out of five patients had statistically significant differences between predicted and actual rectal dose–constraint values, only

one patient (patient A) recorded rectal dose values that were consistently higher than IMRT plan constraints for the rectum. Therefore, although statistical differences in the expected and actual rectal doses were observed, rectal toxicity may not necessarily be of clinical significance to the majority of patients in this study (treated with 74 Gy).

Analysis of the CBCT-generated DVH indicates that not all patients are able to maintain a consistently full bladder, which, again, challenges the reliability of our present bladder instructions to patients. The observation that the bladder volume can potentially decrease to the order of 50% of the planned volume has also

been reported in the literature.<sup>13</sup> Although significant variations in bladder volume were observed for three out of five patients, the planned bladder constraints were seldom violated for any patient. It should also be noted that two out of five patients were able to maintain a relatively consistent bladder with no differences in planned or treated bladder dose.

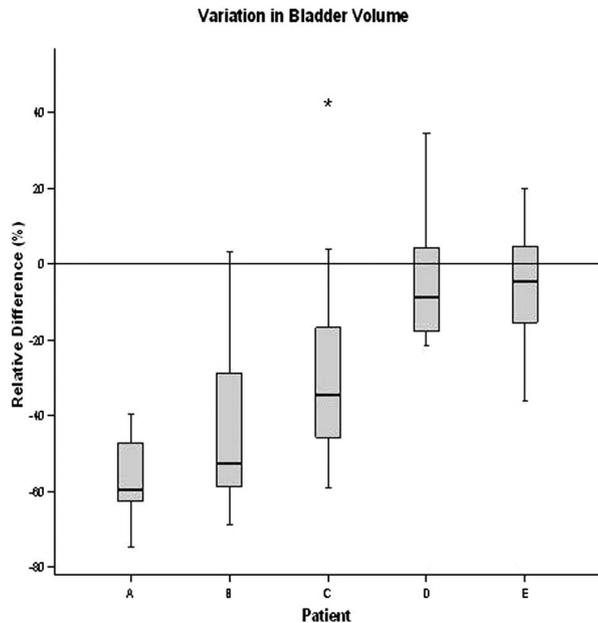


Figure 4. Variation in the bladder volume as contoured on CBCT for patients A–E.

Notes: The horizontal line represents the bladder volume at CT. Abbreviations: CBCT, cone-beam computerised tomography; CT, computerised tomography.

As with any study involving contouring of organs on CT or CBCT, inter- and intra-user variability in delineation of the prostate, rectum and bladder is possible. However, we did attempt to minimise variability by using a standard contouring approach completed by two investigators who received focused training. In the majority of cases, contouring on CBCT datasets was uncomplicated and delineation was completed without issue. However, the presence of rectal gas did cause artefacts that challenged our ability to confidently outline the rectal volume in a minority of patients.

The planning protocol at our institute specifies that the rectum and bladder are contoured as solid organs. The reported variations in volumes are therefore referring to the contents, rather than the wall volumes of the rectum and bladder. From a radiobiological perspective, the walls are the critical structures and the contents are irrelevant in terms of complication risk. Despite acknowledging the differences in volume definitions, we completed all contouring as solid structures because the objective of the project was to report variations in planned versus actual DVH values, and the rectal/bladder dose constraints are based on solid contours.

The results presented in this paper are based on 95 CBCT-based dose distributions from five case studies. The results are therefore not intended to be reflective of the patient population treated at our institution. Nevertheless, this

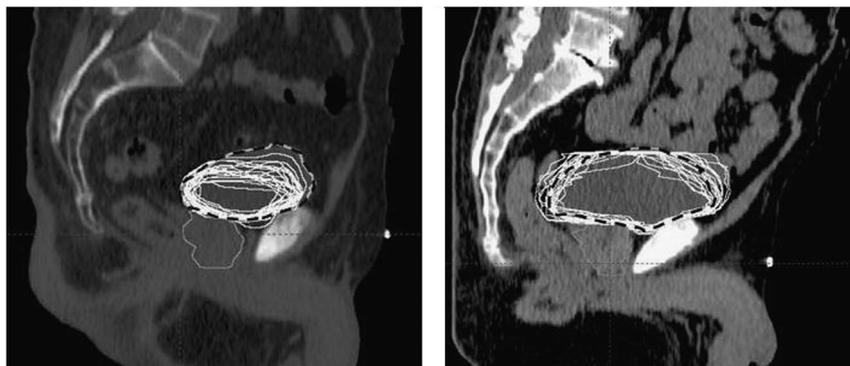


Figure 5. The image on the left shows the bladder for patient A and on the right patient D.

Notes: The bladder volumes as contoured on 19 CBCT images (white contours) are superimposed on the planning CT, with the original bladder volume outlined with black dashed line. The prostate CTV is also shown as faint white line.

Abbreviations: CBCT, cone-beam computerised tomography; CT, computerised tomography; CTV, clinical target volume.

paper does highlight that potential inaccuracies exist in the ability of a single CT-based dose distribution to predict dose delivery in patients treated for localised prostate cancer. The finding that CBCT bladder and rectum volumes can vary significantly indicates that the bowel/bladder protocol used in our department is not consistently successful and improvements in the present preparation instructions are needed.

Further investigation of a larger sample size is warranted to gain a better understanding of the ability of the initial CT-based DVH to predict dose delivery. And finally, the argument for adaptive radiation therapy, whereby the CBCT is used as a dose-guidance and not simply an image-guidance strategy,<sup>14</sup> is further strengthened by the significant variations in rectum and bladder volumes (and dose) observed in this study.

## CONCLUSION

In the context of radiation therapy to the prostate, the CT-based planning DVH should be regarded as only a 'snap shot' of dose delivery to the rectum and bladder. Variations in the bladder and rectal volume did occur, despite the use of a standard protocol. Daily variations in dose delivery to the prostate CTV were minor, whereas dose variations to the rectum and bladder tended to be more significant. In conclusion, predicted dose metrics are not always valid and should therefore be regarded with some degree of caution by the treating physician.

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