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The effects of volumetric changes on radiation doses of the rectum and bladder during radiotherapy in patients with prostate cancer

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► ***Original article***

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ABSTRACT

Background: In prostate radiotherapy, changes in the volume of the bladder and rectum can influence dose delivery. In this study, cone-beam computerised tomography (CBCT) imaging was used to assess volumetric, and corresponding radiation dosimetric changes, for the bladder and rectum in patients with prostate cancer treated using VMAT. ***Materials and Methods***: Treatment planning computed tomography (simCT) and CBCT images were retrospectively evaluated in 22 patients with prostate cancer. Bladder and rectal volumes were recontoured in 176 CBCT images. CBCT images were used for VMAT treatment plan recalculation and to obtain bladder and rectum radiation doses. ***Results:*** Mean rectal volumes measured by CBCT were significantly larger than those estimated by simCT (P=0.001). A 14% increase in rectum volume resulted in a 9% increase in mean rectum doses. The percent volumes (Vx) of the rectum receiving 40, 50, 60 and 70 Gy doses based on CBCT results were significantly larger than those based on simCT results (P=0.002, P=0.001, P=0.001, P 0.003, respectively). Mean bladder volumes measured by CBCT were significantly smaller than those estimated by simCT (P=0.001). A 13% decrease in bladder volume resulted in a 8% increase in mean bladder doses. Mean bladder V65 and V70 values based on CBCT results were significantly higher than those based on simCT results (P<0.001, P=0.002, respectively). ***Conclusion:*** Results during prostate radiotherapy, daily changes in bladder and rectal volumes can result in larger actual doses to these organs than the planned dose.

Keywords: *Cone-beam computerized tomography, dosimetry, prostate cancer, radiotherapy, volumetric modulated arc therapy.*

INTRODUCTION

Approximately 11.6% of men are diagnosed with prostate cancer during their lifetime [1]. However, in almost 90% of patients, the disease is confined to the prostate and their 5-year survival rate approaches 100% [2]. Due to this high survivorship, adverse effects associated with prostate cancer treatment have a profound effect on quality of life characteristics [3].

Radiotherapy (RT) is a well-established treatment modality for the management of localised prostate cancer. Most of the RT-associated acute side effects resolve within 2–4 weeks [2]. However, long-term side effects may last more than 6 weeks and are frequently assessed using the Radiation Therapy Oncology Group (RTOG) scoring system [4, 5]. Associations between RT-related toxicity and time, dose, and volume are evaluated using the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) scale [6].

Current dose recommendations for prostate cancer include 75.6–81 Gy for primary RT with standard fractionations; 64–72 Gy is recommended for adjuvant RT [7]. Before the use of 3-dimensional conformal RT (3D-CRT), the prescribed dose of primary RT was limited to 70

Gy due to the risk of rectal and bladder toxicity [8]. Use of intensity-modulated radiation therapy (IMRT) now allows maximizing the prescribed dose to the prostate while minimizing the exposure to the surrounding tissue. Volumetric modulated arc therapy (VMAT) is a radiation technique that has shorter beam-on time and more homogenous dose distributions compared with IMRT [9]. Radiotherapy treatment planning should consider internal organ movements, which can result in a lower dose to the prostate and a higher dose to the surrounding tissues. Daily cone-beam computerised tomography (CBCT) verification can be used during IMRT and VMAT to assess internal organ movements and minimise daily setup errors [10,11]. Actual doses delivered to the target and critical structures can be assessed with CBCT [12,13].

Bladder and rectal volumes can change during RT [14]. A mean percent volume changes in bladder and rectum can result in changes in the percentage of the dose calculated for these two organs [15]. Use of a dose-volume histogram (DVH) to evaluate these changes revealed that the actual doses received by the rectum and bladder are higher than the planned doses, as calculated by 3D computed tomography simulation (simCT) images [16].

The aim of this study was to assess the effects of volumetric changes on the radiation doses of the bladder and rectum and to estimate a potential effect on dose change. This study used the method of superimposing treatment plans onto weekly CBCT images of patients with prostate cancer undergoing VMAT.

MATERIALS AND METHODS

Patient selection

The simCT images, treatment plans, and CBCT images of 22 prostate cancer patients treated at our clinic were assessed using a retrospective analysis. To be included in the study, patients must have completed a primary or salvage RT for prostate cancer from Janury 2016 to August 2017 and received treatment planning for VMAT. Patients were excluded from the study population if they had received hybrid treatment planning for VMAT and 3D-CRT.

The study was approved by the institutional ethics committee.

Simulation and treatment

Patients were instructed to empty their rectum and bladder, drink 500 ml water, and wait 1 hour. Then patients were scanned (simCT, Aquilion-LB, Toshiba, Japan) while in the supine position with the arms placed on the chest. Images were obtained using an adjacent axial slice spacing of 2 mm without intravenous contrast. The entire pelvis, from the upper abdomen to the bottom of the perineum, was included in the image. SimCT imaging was repeated after defecation of patients with excessive rectum filling.

Three treatment volumes were used as followed: small field RT (SFRT) in 7 patients, postoperative SFRT in 8 patients and pelvic treatment followed by SFRT in 7 patients. For patients with radical RT, the prostate and seminal vesicles were contoured as the clinical target volume (CTV) and this treatment volume was described as SFRT. For patients with salvage RT, the CTV of the SFRT included the prostate and seminal vesicle bed. For postoperative SFRT RTOG contouring atlas was used as the reference [17]. The planning target volume (PTV) of SFRT was created using a 5-mm posterior margin and an 8-mm margin in all other directions. Pelvic treatment delivered to the prostate and pelvic lymph nodes, followed by a SFRT boost. The superior border of the pelvic treatment CTV was at the L5/S1 interspace and the obturator, external iliac, internal iliac, and S1-2 sacral lymph nodes were included. The PTV of pelvic treatment was defined as CTV plus 5 mm in all directions. The bladder, the rectum from the anal canal to the sigmoid curve, each bilateral femoral head, and the small intestine surrounding the PTV were outlined as the organs at risk (OARs).

Treatment planning

Overall, 22 patients received 38-41 fractions of RT with 1.8-2 Gy per fraction. Eleven patients

were presicribed total doses of 76 to 78 Gy with daily fraction of 2 Gy in 38-39 fractions delivered over 7.5 weeks. Three patients had radiotherapy with a total dose of 74 Gy with daily fraction of 1.8 Gy per fraction. Eight patients with biochemical failure after prostatectomy had salvage radiotherapy with total presicribed doses of 70.2 to 72 Gy by 1.8 Gy per fraction. Pelvic treatment delivered 45 to 46 Gy with 1.8-2 Gy per fraction followed by a SFRT boost to achieve total presicribed doses of 74 to 78 Gy.

VMAT plans were created using 6 MV photon energy and a double arc (CMS Monaco 5.1 treatment planning system). For each plan, 98% of the target volume was covered by 95% of the prescribed dose. OARs doses were kept below the QUANTEC tolerance limits [6].

Cone-beam computerised tomography

All patients undergoing RT for prostate cancer at our clinic were assessed using daily CBCT images (Elekta XVI Pelvis M20 imaging protocol). During the treatment of the patients, daily CBCT images were assessed by bone tissue matching. Due to the difficulty in assessing a high number of daily images, the CBCT image obtained during the first fraction was accepted as the CBCT image for week 1 for each patient. A total of 176 images taken at 1-week intervals were assessed during a period of 8 weeks. The bladder and the rectum from the anal canal to the sigmoid curve were contoured in each CBCT.

CBCT and simCT images were matched with using fusion method. Bone tissue matching was used as a fusion method to achieve similar effect with actual treatment. Before the calculation was performed CBCT electron density (ED) information was specified in the treatment planning system for Elekta XVI Pelvis M20 imaging protocol. The original treatment plans were recalculated in the same isocentre for each patient's CBCT images.

Statistical analyses

SPSS version 21 software (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. The planned and weekly dose parameters were tested using the paired t-test. One-way analysis of variance with independent samples was used to analyse changes in the bladder and rectum volumes for each patient. Mann-Whitney U test and Wilcoxon signed rank test were performed to analyse the dose and volume variations for primary and salvage radiotherapy groups. Friedman test was used for non-parametric variables. A $P < 0.05$ was considered statistically significant.

RESULTS

The simCT and CBCT results indicated that the mean ± standard deviation values for rectal volume were 97.42 ± 41.65 cc and 104.20 ± 29.32 cc, respectively (P =0.001). The results of the weekly CBCT plans indicated that rectal volume ranged from 302.09 cc to 34.06 cc (P =0.66). Figure 1 presents the axial cross-sectional images and dose-volume histograms for the rectal contours superimposed onto the corresponding simCT images in the two patients with the greatest and smallest changes in rectal volume during the 8-week CBCT imaging period.

A 14% increase in rectum volume resulted in a 9% increase in mean calculated rectum doses. The mean dose (Dmean) calculated for the rectum was 40 Gy with simCT and 44 Gy with CBCT (P =0.03). The percent volumes (V_x) of the rectum receiving 40, 50, 60 and 70 Gy doses based on the CBCT results were significantly greater than those based on the simCT results (P= 0.002, P =0.001, P =0.001, and P =0.003, respectively) (table 1). Assessment among the weekly CBCT plans revealed no statistically significant changes in V_{40}, V_{50}, V_{60} and V_{70} values of the rectum (P =0.27, P =0.14, P =0.08, and P =0.08, respectively) (figure 2).

The treatment presicribed total doses were 76 to 78 Gy in 11 out of 22 patients. The percent volumes (V_x) of the rectum receiving 75 Gy doses were assessed only in those 11 patients. The mean values for V_{75} estimated from simCT and CBCTs' were 5% (0.3%-10%) and 13% (5%-39%), respectively (P =0.03).

The mean ± standard deviation values for

bladder volume estimated from simCT and CBCT were 358 ± 141.31 cc and 291.21 ± 113.38 cc, respectively (P =0.001). Comparison of the weekly CBCT results with the simCT results revealed a statistically significant decrease in bladder volume from week 4 to week 8 (P =0.006, P =0.026, P =0.003, P =0.015 and P =0.001, respectively). Results of an assessment of weekly CBCT plans indicated that the bladder volume ranged from 747.35 cc to 77.61 cc (P =0.047). Figure 3 presents the transverse cross-sectional images and dose-volume histograms for the bladder contours superimposed onto the corresponding simCT images in the two patients with the greatest and smallest changes in bladder volume during the 8 -week CBCT imaging period.

A 13% decrease in bladder volume resulted in a 8% increase in mean calculated bladder doses. The bladder Dmean values estimated using simCT and CBCT were 45 Gy and 49 Gy, respectively (P= 0.001). The bladder V_{65} and V_{70} values based on the CBCT results were significantly higher than those based on the simCT results (P= 0.001 and P =0.002, respectively) (table 1). An assessment among the CBCT plans revealed no significant changes in bladder V_{65} an V_{70} values (P =0.5) (figure 4).

Radiotherapy was given 14 out of 22 patients as an aim of primary treatment. In this group, the mean ± standard deviation values for bladder volume estimated from simCT and CBCT were 367.97 ± 141.43 cc and 300.06 ± 128.83 cc, respectively (P =0.004). The bladder Dmean values estimated using simCT and CBCT were 43 Gy and 47 Gy, respectively (P =0.013). The bladder V_{65} and V_{70} values based on the CBCT results were significantly higher than those based on the simCT results (P 0.048 and P 0.048, respectively) (table 2).

Eight patients were received salvage radiotherapy following by surgery. In this group, the mean ± standard deviation values for bladder volume estimated from simCT and CBCT were 344.43 ± 158.33 cc and 284.86 ± 92.79 cc, respectively (P =0.12). The bladder Dmean values estimated using simCT and CBCT were 49 Gy and 51 Gy, respectively (P 0.48). The bladder V_{65} and V_{70} values based on the CBCT results were not significantly higher than those based on the simCT results (P =0.67 and P =0.069, respectively) (table 2).

Comparison of primary and salvage radiotherapy results were not statistically significant for bladder volumes on simCT and CBCT images (P= 1 and P= 0.89, respectively). The bladder Dmean values estimated using simCT and CBCT were not significantly different between these groups (P =0.11, P =0.41, respectively). In patients treated with salvage radiotherapy, the bladder V_{65} and V_{70} values based on the simCT results were significantly higher relative to those treated with primary radiotherapy (P= 0.005 and P =0.024, respectively). However, based on CBCTs' calculations, differences of V_{65} and V_{70} values did not reach statistical significance between the groups receiving primary and salvage radiotherapy (P =0.076, P =0.13, respectively).

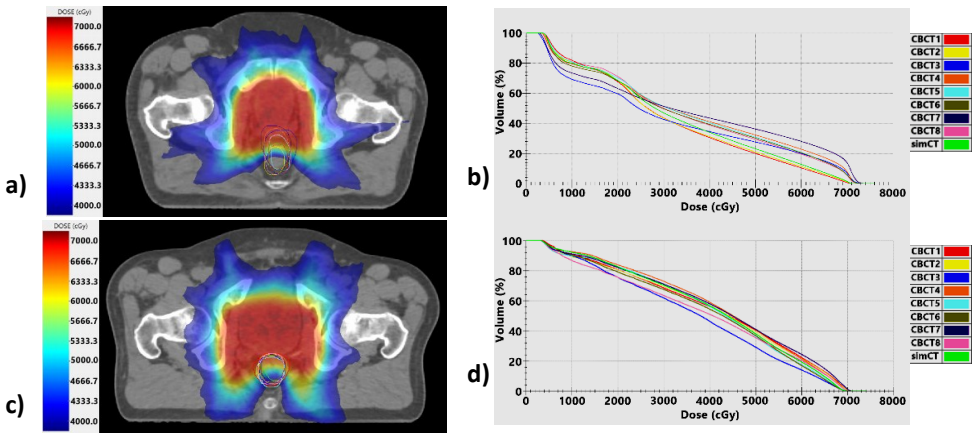

Figure 1. The effects of volumetric changes on radiation doses of the rectum and bladder during radiotherapy in patients with prostate cancer.

Table 1. Mean rectal and bladder percent volumes (Vx) obtained from 3D treatment-planning computed tomography (simCT) compared with cone-beam computed tomography (CBCT).

	simCT (%)	CBCT (%)	% change	*P* value
Rectum				
V_{40}	52	57	5	0.002
V_{50}	35	41	6	0.001
V_{60}	22	30	8	0.001
V_{70}	9	18	8	0.003
Bladder				
V_{65}	29	35	6	<0.001
V_{70}	22	28	6	0.002

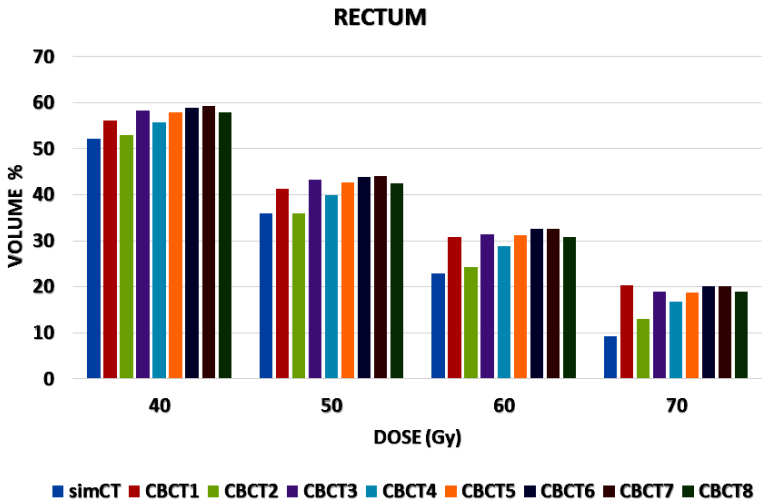

Figure 2. The effects of volumetric changes on radiation doses of the rectum and bladder during radiotherapy in patients with prostate cancer.

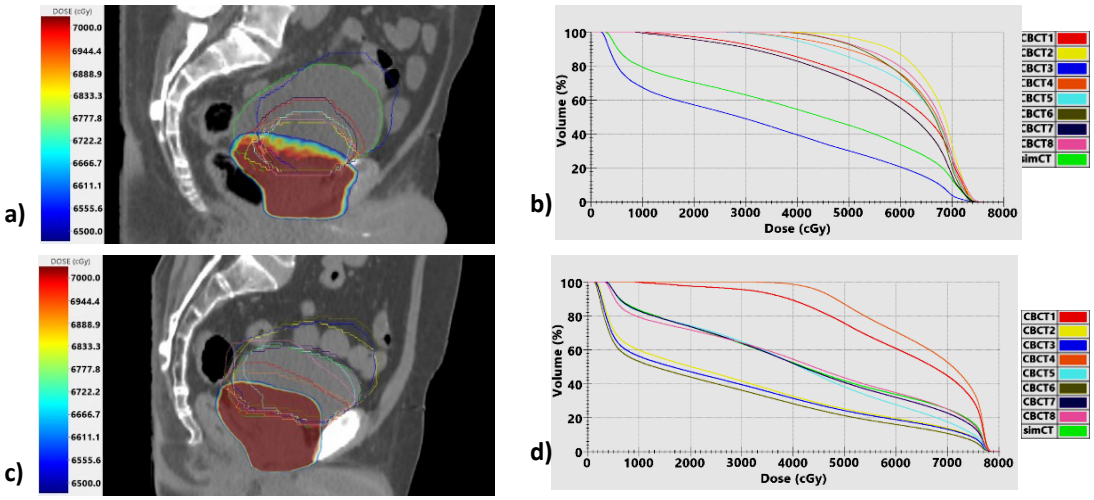

Figure 3. The effects of volumetric changes on radiation doses of the rectum and bladder during radiotherapy in patients with prostate cancer.

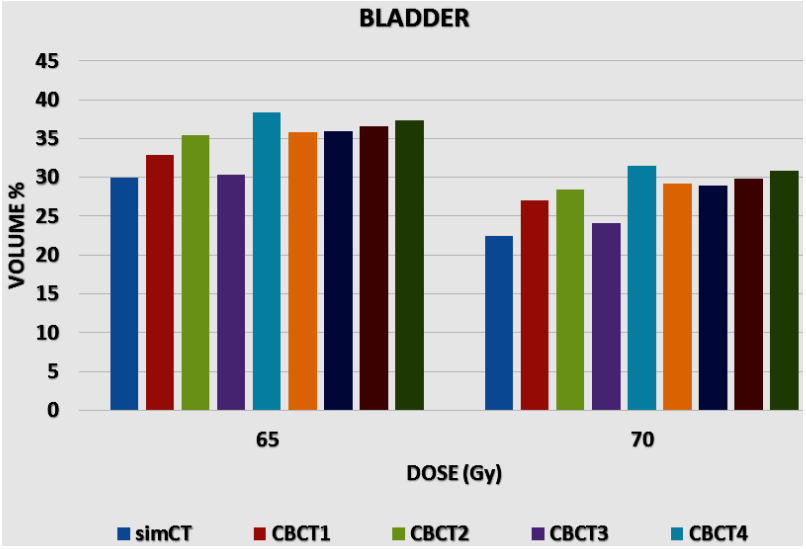

Figure 4. The effects of volumetric changes on radiation doses of the rectum and bladder during radiotherapy in patients with prostate cancer.

Table 2. Mean bladder percent volumes (Vx) comparission of prostate cancer patients with primary and salvage radiotherapy. simCT: 3D treatment-planning computed tomography; CBCT: cone-beam computed tomography.

	simCT (%)	CBCT (%)	% change	*P* value
Primary RT				
V_{65}	23	30	7	0.048
V_{70}	18	25	7	0.048
Salvage RT				
V_{65}	40	43	3	0.670
V_{70}	28	33	5	0.069

DISCUSSION

Previous studies comparing simCT images with CT images have found that the integral rectal dose increases by a factor ranging from 1.3 to 2.1. This increase was attributed to rectal volume expansion or internal prostate movement that changes rectal filling [18,19].

Huang *et al*. contoured prostate, rectal, and bladder volumes for 112 CBCT images. They found that changes in the mean values for rectal and bladder volumes of 36% and 20% resulted in mean dose changes of 22% and 2%, respectively [15]. In our study, treatment plans based on simCT were copied onto CBCT images to provide a combined assessment of internal and external setup uncertainty. We found that changes in the mean values for rectal and bladder volumes of 14 % and 13 % resulted in mean dose changes of 9 % and 8 %, respectively.

Chen *et al.* copied the original planning based on simCT onto the CBCT image to recalculate the dose. The results indicated that a 10% increase in bladder volume resulted in a 5.6% decrease in the mean bladder dose [20]. In our retrsopective study, bladder volume decreased during the treatment. A statistically significant decrease in bladder volume revealed from week 4 to week 8.

Caseres-Magas *et al.* examined only bladder volume change and found that it was statistically significant, even in patients who underwent a full bladder/daily image-guided protocol. However, there were no statistically significant differences in any DVH parameter at any dose level tested [21]. In our study, although all patients were simulated and treated with a full bladder, DVH parameters measured on CBCT during treatment were found to be higher than those planned on simCT.

Akin *et al.* assessed the effects of bladder and

rectal changes on DVH parameters in 20 patients who underwent post-prostatectomy RT. They found that the change in rectal or bladder volume had no statistically significant effects on the DVH results [16]. In our study, patients who underwent primary radiotherapy and salvage radiotherapy were compared according to their bladder volumes. Although there was no difference between the two groups in bladder volume on simCT, the V_{65} and V_{70} values which calculated during treatment planning were found to be higher in patients receiving salvage radiotherapy. However, patients treated with primary radiotherapy had more changes on DVH parameters during treatment relative to those treated with salvage radiotherapy.

In all patients, VMAT planning was performed to achieve rectal and bladder doses below the tolerance levels as specified by QUANTEC. Patients were assessed using daily CBCT during the treatment period. When patients failed to achieve adequate bladder filling, the waiting time was extended, and the rectum was emptied if it was full enough to displace the prostate outside the PTV. Our results indicated that the current patient instruction which used as in our clinic was not sufficient to ensure the empty rectum and full bladder. Radiotherapy treatment planning should consider increases in tolerance doses of 5% for V_{40}, 6% for V_{50}, and 8% for V_{60}, V_{70} and V_{75} for the rectum, and 8% for V_{65} and V_{70} for the bladder.

This study contained some limitations. The first one was the retrospective design of the study and the second one was the use of weekly CBCT images during radiotherapy. Future prospective studies with evaluation of daily CBCT images could give us more information about actual doses of OARs.

During prostate radiotherapy, the actual doses of the bladder and rectum were significantly larger than the planned dose. Radiation oncology clinics are advised to assess volumetric and dosimetric changes throughout radiotherapy in patients with prostate cancer to minimize toxicity to the surrounding tissues.

***Conflicts of interest*:** *Declared none.*

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