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# The Impact of Variation in Bladder Volume on the Doses of Target and Organ-at-Risk in Intensity-Modulated Radiation Therapy for Localized Prostate Cancer

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## Abstract

Intensity-modulated radiation therapy (IMRT) has become the mainstay of treatment for localized prostate cancer. In IMRT, minimizing differences between the conditions used during planning CT and daily treatment is important to prevent adverse events in normal tissues. In the present study, we evaluated the impact of variation in bladder volume on the doses to various organs. A total of 35 patients underwent definitive radiotherapy at Saitama Medical Center. A Light Speed RT16 (GE Healthcare) was used for planning and to obtain examination CT images. Such images were acquired after 4 - 6 days of planning CT image acquisition. The IMRT plans were optimized using the planning CT data to satisfy the dose constraints set by our in-house protocols for the PTV and the OARs. The dose distributions were then re-calculated using the same IMRT beams, and checked on examination CT images. It was clear that bladder volume affected the doses to certain organs. We focused on the prostate, bladder, rectum, small bowel, and large bowel. Regression coefficients were calculated for variables that correlated strongly with bladder volume ($p < 0.05$). We found that variation in bladder volume [cm$^3$] predicted deviations in the bladder $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$ [%]; the maximum dose to the small bowel [cGy]; and the maximum dose to the large bowel [cGy]. The regression coefficients were −0.065, −0.125, −0.180, −10.22, and −9.831, respectively. We evaluated the impacts of such variation on organ doses. These may be helpful when checking a patient's bladder volume before daily IMRT for localized prostate cancer.

**Keywords**

Bladder Volume, Localized Prostate Cancer, Intensity-Modulated Radiation Therapy, Dose to Organs at Risk, Computed Tomography

## 1. Introduction

Prostate cancer is the most common cancer in men, and intensity-modulated radiation therapy (IMRT) has become the mainstay of treatment for localized prostate cancer. IMRT delivers radiation more precisely than earlier techniques, sparing surrounding normal tissue [1]. In IMRT, an inverse planning technique is used to optimize the dose distribution. Such optimization is performed with the aid of computed tomography (CT) images. However, daily variations in organ conditions are not considered when calculating the doses delivered to organs at risk (OARs). Therefore, minimizing the differences between organ conditions during planning CT and those during daily treatment is important to prevent adverse events in normal tissues.

In the present study, we evaluated the impact of variation in bladder volume (the amount of urine) on the target and OAR doses during localized prostate IMRT. One possible advantage of maintaining a full bladder is that part of the bladder moves away from the target volume, thereby reducing bladder toxicity [2] [3]. A full bladder also moves the small and large bowels out of the irradiation field, reducing toxicity to these organs [4]-[8]. However, if large bladder volumes are used during CT planning and radiotherapy, such volumes tend to exhibit marked variability [9]-[11]. Thus, a bladder volume of about 150 $cm^3$ is more suitable for planning [12], and it is important to confirm that the bladder volume during daily treatment is the same.

Transabdominal bladder ultrasound devices and in-room CT techniques (e.g., kV Cone-beam CT, MV Cone-beam CT, and On-rail CT) can be used to measure bladder volume [2]-[14]. In-room CT increases the doses to normal tissues. In contrast, ultrasound techniques are non-invasive, rapid, and inexpensive [9] [10] [13]; they are thus useful when checking the bladder volume in patients undergoing localized prostate IMRT. Given the time constraints of clinical practice, it is difficult to perfectly equalize the bladder volume during radiotherapy to that during planning CT. Criteria for determining whether to take any action, such as extending the urine collection time, are required. However, no previous report has focused on the impact of bladder volume variation on target and OAR doses during IMRT for localized prostate cancer. We therefore addressed the topic.

## 2. Methods and Materials

### 2.1. Patients and CT Image Acquisition

Between June 2015 and May 2016, 35 patients underwent definitive radiotherapy at Saitama Medical Center. All procedures used in this research were approved by the

Ethical Committee of Saitama Medical Center. Table 1 shows the patient characteristics. The patients were irradiated in a supine position with the aid of a thermoplastic seat (Figure 1). A Light Speed RT16 (GE Healthcare, Little Chalfont, UK) was used for planning CT and acquisition of the examination CT images used to determine the reproducibility of organ conditions (4 - 6 days after planning CT image acquisition). Body surface markers placed at the time of planning CT image acquisition were used to align the CT images (2.5 mm in slice thickness). Patients were instructed to drink a fixed volume of water 30 - 60 min before CT image acquisition; urination was prohibited to enable appropriate acquisition. The CT images were examined for rectal gas by a radiation oncologist. If necessary, additional CT images were acquired based on the recommendation that the diameter of the rectum, measured transversely at the base, should be >4 cm [15]. Cone-Beam CT images have been used for evaluation of the

Figure 1. The thermoplastic seat used to immobilize the patients.

Table 1. Patient characteristics.

| | | Data |
|---|---|---|
| **Age** | Median | 78 |
| | Range | 53 - 84 |
| **Clinical stage** | T1 | 6 |
| | T2 | 15 |
| | T3 | 12 |
| | T4 | 2 |
| **PSA** | Mean | 29.8 |
| | Range | 4.3 - 220.9 |
| **Gleason score** | ≤7 | 12 |
| | 8 | 14 |
| | ≥9 | 9 |

variations in organ conditions in several reports [14] [16]. However, the dose calculation using Cone-Beam CT images are required the CT values corrections [17]-[19], so the uncertainty of the dose calculation using Cone-Beam CT images is greater than that using Fan-Beam CT images. Additionally, Fan-Beam CT image qualities are higher than Cone-Beam CT image qualities. Thus, Fan-Beam CT images were used for evaluation in this study.

## 2.2. Contours

XiO version 5.00 (Elekta, Stockholm, Sweden) was the Radiation Treatment Planning System (RTPS) used. Target and organ volumes were determined, based on the planning CT images, by a radiation oncologist and a medical physicist. **Figure 2** shows the example of target and organ volumes determined in this study. A prostate clinical target volume (CTV) and planning target volume (PTV) were defined. The CTV was the prostate with 10 mm of the proximal seminal vesicle. All seminal vesicles were included in the CTV (in cases of clinical T3b stage disease). PTV was defined as the CTV plus a 10 mm margin (rectal side: 5 mm). The OARs were the rectum (from the ischial tuberosities to the rectosigmoid flexure), the rectal wall within 10 mm above and below the PTV (wall thickness: 4 mm), the bladder, the bladder wall (wall thickness: 4 mm), and the small and large bowels. The bladder volume was calculated using the planning CT images.

## 2.3. Planning

The linac model of Clinac 21EX (Varian Medical Systems, Palo Alto, CA; X-ray energy: 10 MV) was used for planning. Step-and-shoot IMRT plans were created based on the planning CT images using seven coplanar photon beams (gantry angles: 0˚, 50˚, 100˚, 145˚, 215˚, 260˚, and 310˚). The prescribed dose to 95% of the PTV was 74 Gy in 37 fractions. The dose calculation grid size was always set to 2 mm. The iso-center was the center of the prostate. Superposition [20] [21], with heterogeneous correction, was used as the dose calculation algorithm.

**Table 2** shows the dose constraints employed. The treatment plans were optimized to satisfy constraints defined by our in-house protocols for doses to the PTV and OARs.

## 2.4. Re-Calculation Using Examination CT Images

Target and organ volumes were determined, based on the examination CT images, by a radiation oncologist and a medical physicist. The bladder volumes on the examination CT images, and the relative variations in such volumes between the planning and examination CT images, were calculated using the formula below. $V_{b\text{-}c}$ is the bladder volume on examination CT and $V_{b\text{-}p}$ the bladder volume on planning CT (for the same patient). Dose distributions were then re-calculated using the examination CT images and the same IMRT beams described above. The iso-center was set at the coordinates indicated by planning CT.

$$\text{Bladder volume variation}\left[\text{cm}^3\right] = V_{b\text{-}c} - V_{b\text{-}p}$$

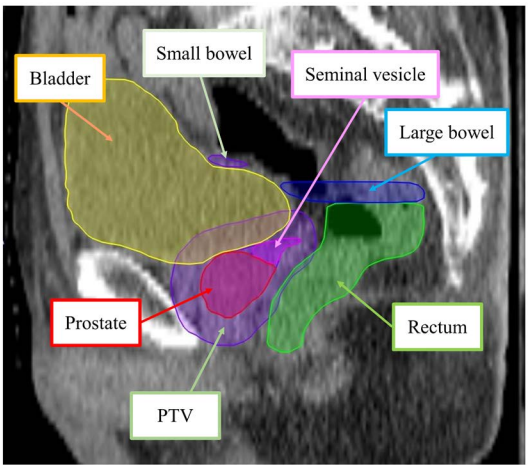


**Figure 2.** The example of target and organ volumes determined in this study.

**Table 2.** Dose constraints used in this study.

| Contour | Index | Optimal |
|---|---|---|
| **PTV** | $D_{95\%}$ [Gy] | >74 |
| | Mean dose [Gy] | 73.26 - 76.22 |
| | $D_{max}$ [Gy] | <79.18 |
| | $V_{98\%}$ [%] | >98 |
| **Rectum** | $V_{65Gy}$ [%] | <17 |
| | $V_{40Gy}$ [%] | <35 |
| | $V_{20Gy}$ [%] | <60 |
| **Rectal wall** | $V_{78Gy}$ [%] | <1 |
| | $V_{70Gy}$ [%] | <20 |
| | $V_{60Gy}$ [%] | <30 |
| | $V_{40Gy}$ [%] | <60 |
| **Bladder** | $V_{54Gy}$ [%] | <25 |
| | $V_{33Gy}$ [%] | <50 |
| **Bladder wall** | $V_{70Gy}$ [%] | <35 |
| | $V_{40Gy}$ [%] | <60 |
| **Small bowel** | $V_{60Gy}$ [$cm^3$] | <0.5 |
| **Large bowel** | $V_{65Gy}$ [$cm^3$] | <0.5 |

## 2.5. Evaluation of the Target Volume Dose

The coordinates of the center of the prostate (left-right, superior-inferior, and anterior-posterior) and those of the CTV doses ($D_{98\%}$ and $V_{90\%}$) were compared between the planning and examination CT images, and deviations calculated using the RTPS. The impacts of bladder volume variation on prostate position and CTV dose were explored. Pearson correlation coefficients ($r$) with $p$-values were calculated. A difference was

considered significant if the two-tailed $p$-value was <0.05. SPSS version 23 software (IBM Corp., Armonk, NY) was used for statistical analysis.

### 2.6. Evaluation of the Doses to OARs

The doses to the bladder (maximum dose [$D_{max}$], $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$), bladder wall ($D_{max}$, $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$), rectum ($D_{max}$, $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$), rectal wall ($D_{max}$, $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$), and the small and large bowel ($D_{max}$ values) were calculated using the RTPS; deviations were also calculated using the RTPS. The impact of bladder volume variation on doses to the OARs was explored. Pearson correlation coefficients ($r$) with $p$-values were calculated. A difference was considered significant if the two-tailed $p$-value was <0.05. SPSS version 23 software (IBM Corp.) was used for statistical analysis.

### 2.7. Linear Regression

We subjected variables that correlated strongly with bladder volume ($p < 0.05$) to a regression analysis and calculated regression coefficients with 95% confidence intervals (CIs). SPSS version 23 software (IBM Corp.) was used for statistical analysis.

## 3. Results

The mean bladder volume (±1 standard deviation) was 191 mL (±93 mL) on planning CT and 148 mL (±81 mL) on examination CT.

Table 3 shows the outcomes of a univariate analysis of associations with variation in bladder volume. Such variation predicted deviations in the bladder $V_{30Gy}$ - $V_{70Gy}$, the bladder wall $V_{30Gy}$ - $V_{70Gy}$, and the small and large bowel $D_{max}$ values. In contrast, variation in bladder volume did not predict deviations in the doses to the prostate or the CTV, the bladder $D_{max}$, the bladder wall $D_{max}$, or the rectum or rectal wall doses.

Table 4 lists the regression coefficients between bladder volume variation and each dependent variable. Figure 3 shows the deviations in the bladder and the bladder wall $V_{70Gy}$, $V_{50Gy}$, and $V_{30Gy}$ as functions of bladder volume variation. The regression coefficients (with 95% CIs) were −0.065 (−0.088 to −0.042), −0.125 (−0.154 to −0.096), −0.180 (−0.211 to −0.149), −0.054 (−0.069 to −0.038), −0.099 (−0.121 to −0.078), and −0.152 (−0.178 to −0.125), respectively. Figure 4 shows the deviations in the small and large bowel $D_{max}$ values as functions of bladder volume variation. The regression coefficients (with 95% CIs) were −10.22 (−15.69 to −4.743) and −9.831 (−13.96 to −5.702), respectively. Thus, a smaller bladder increased the dose to the OARs.

## 4. Discussion

The mean bladder volume during planning CT was larger than that during examination CT. Creation of a thermoplastic seat and body surface marking were required for planning CT, so the patient set-up time was longer than for examination CT. We did not engage in detailed verification; however, the observed difference in bladder volume may be attributable to the longer patient set-up time for planning CT.

**Table 3.** Univariate analysis of associations with variation in bladder volume [cm$^3$].

| Variable | | *r* | *p* |
|---|---|---|---|
| **Coordinates of the prostate center** | L-R [cm] | 0.034 | N.S. |
| | S-I [cm] | −0.076 | |
| | A-P [cm] | −0.045 | |
| **CTV** | $D_{98\%}$ [Gy] | −0.067 | N.S. |
| | $V_{90\%}$ [%] | −0.018 | |
| **Bladder** | $D_{max}$ [Gy] | 0.005 | N.S. |
| | $V_{70Gy}$ [%] | −0.775 | <0.01 |
| | $V_{50Gy}$ [%] | −0.861 | <0.01 |
| | $V_{30Gy}$ [%] | −0.910 | <0.01 |
| **Bladder wall** | $D_{max}$[Gy] | −0.050 | N.S. |
| | $V_{70Gy}$[%] | −0.810 | <0.01 |
| | $V_{50Gy}$[%] | −0.868 | <0.01 |
| | $V_{30Gy}$[%] | −0.902 | <0.01 |
| **Rectum** | $D_{max}$ [Gy] | 0.019 | N.S. |
| | $V_{70Gy}$ [%] | 0.115 | |
| | $V_{50Gy}$ [%] | 0.036 | |
| | $V_{30Gy}$ [%] | −0.018 | |
| **Rectal wall** | $D_{max}$ [Gy] | −0.027 | N.S. |
| | $V_{70Gy}$ [%] | 0.012 | |
| | $V_{50Gy}$ [%] | −0.027 | |
| | $V_{30Gy}$ [%] | −0.011 | |
| **Small bowel** | $D_{max}$ [cGy] | −0.629 | <0.01 |
| **Large bowel** | $D_{max}$ [cGy] | −0.641 | <0.01 |

*L-R: left-right; S-I: superior-inferior; A-P: anterior-posterior; N.S.: not significant.

**Table 4.** Regression coefficients between bladder volume variation [cm$^3$] and the dependent variables.

| OAR | Index | Regression coefficient (95% CI) |
|---|---|---|
| **Bladder** | $V_{70Gy}$ [%] | −0.065 (−0.088, −0.042) |
| | $V_{50Gy}$ [%] | −0.125 (−0.154, −0.096) |
| | $V_{30Gy}$ [%] | −0.180 (−0.211, −0.149) |
| **Bladder wall** | $V_{70Gy}$ [%] | −0.054 (−0.069, −0.038) |
| | $V_{50Gy}$ [%] | −0.099 (−0.121, −0.078) |
| | $V_{30Gy}$ [%] | −0.152 (−0.178, −0.125) |
| **Small bowel** | $D_{max}$ [cGy] | −10.22 (−15.69, −4.743) |
| **Large bowel** | $D_{max}$ [cGy] | −9.831 (−13.96, −5.702) |

We did not find a significant association between prostate position and variation in bladder volume. Similarly, we found no significant association between the dose to the CTV and bladder volume variation. Therefore, if the chosen margin allows for inter-fractional errors in other factors (e.g., set-up error), the impacts of bladder volume variation on target position and dose may be negligible.

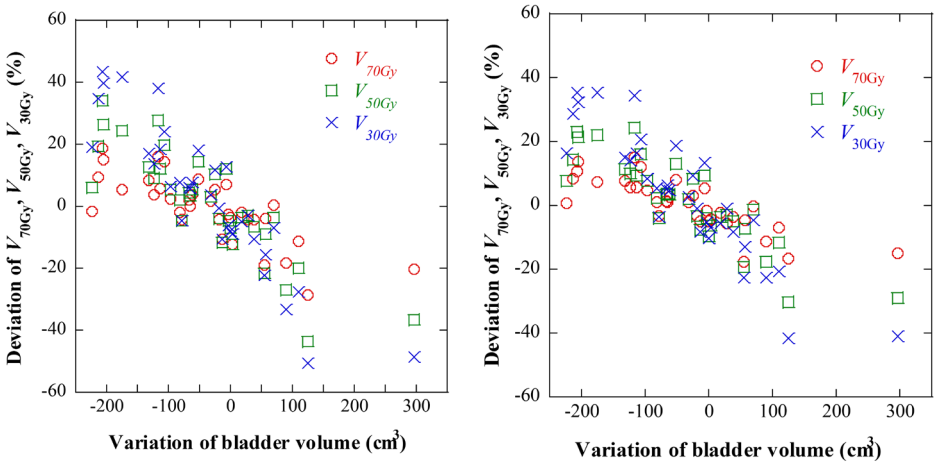


**Figure 3.** The relationship between variation in bladder volume and deviation in bladder dose (Left: Bladder; Right: Bladder wall).

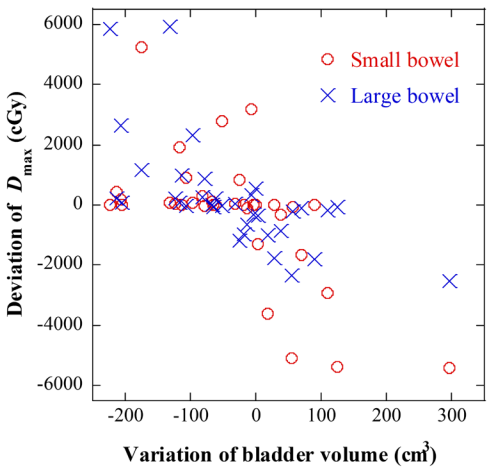


**Figure 4.** The relationship between variation in bladder volume and deviations in the small and large bowel $D_{max}$ values.

For the rectum and rectal wall, we found no significant association between the $D_{max}$ and $V_{30Gy}$ - $V_{70Gy}$ and bladder volume deviation. Thus, the impact of such variation on the rectal dose may be negligible.

For the bladder and bladder wall, we found no significant association between the $D_{max}$ values and bladder volume variation. As part of the bladder overlapped with the PTV in all cases, the bladder $D_{max}$ and the dose to the internal region of the PTV were approximately equal. Additionally, the treatment plans were optimized to render the internal PTV dose uniform. Therefore, the bladder $D_{max}$ was not significantly affected by bladder volume variation. On the other hand, we did find significant associations between the bladder and bladder wall $V_{30Gy}$ - $V_{70Gy}$ values and bladder volume variation. The smaller the bladder, the greater the proportion of the bladder that lies near the tar-

get volume. Therefore, a reduction in bladder volume increases the bladder dose, and it is thus important to check that the bladder volume during daily treatment is greater than that during planning CT.

For both the small and large bowel, we found significant associations between the $D_{max}$ values and bladder volume variation. A smaller bladder moves the small and large bowel near the irradiation field [4]-[8] and increases the doses to these organs. A previous report showed that TD 50/5 of small bowel was 60 Gy (for 1/3 of the volume) and TD 50/5 of large bowel was 65 Gy (for 1/3 of the volume) [2]. It is thus important to check that the bladder volume during daily treatment is greater than that during planning CT. Additionally, it is also important to check that the doses of small and large bowel are <60 Gy and 65 Gy, respectively. If the amount of urine is inadequate, an extension of time to allow urine to collect in the bladder should be considered to reduce the doses to these organs. The criteria whether the amount of urine is adequate can be decided by using the bladder volume and the doses to the OARs during planning CT, the dose constraints, and the regression coefficients in this study.

No previous report has quantitatively evaluated the effects of bladder volume variation on organ doses during IMRT for localized prostate cancer. We found that variation in bladder volume predicted deviations in the bladder $V_{30Gy}$ - $V_{70Gy}$, bladder wall $V_{30Gy}$ - $V_{70Gy}$, and small and large bowel $D_{max}$ values. The absence of a bladder volume check may increase the doses to OARs. An ultrasound device can be used to measure bladder volume non-invasively, rapidly, and inexpensively [9] [10] [13]. Such a device should be used to check the bladder volume prior to daily localized prostate IMRT; this is very important. Our results may be useful when choosing an appropriate bladder volume for each patient.

## 5. Conclusion

We evaluated the effect of bladder volume variation on organ doses, and we developed bladder volume criteria. Our results may be useful when checking the bladder volume before daily IMRT for patients with localized prostate cancer.

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