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Treatment Planning Volume According to Change in Bladder Volume in Therapy of Proton Beam in Magnetic Field

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The purpose of this study was to investigate the changes of bladder volume before therapy of proton beam in magnetic field, and to estimate the target volume (PTV) margin to be considered in treatment planning. Thirty patients with prostate cancer were included in this study. Three gold fiducial markers were attached to the prostate to confirm the position of the prostate by pretreatment X-ray. The urine was completely emptied 1 hour and 30 minutes before the CT-Simulation, and the urine was confirmed by ultrasonography. The bladder was filled with 500 cc of water. Bladder volume was measured by CT scans after treatment. On the first day of treatment, 30 patients underwent the same pretreatment as in CT-Simulation, and their bladder volume was obtained using ultrasound during the 25th treatment, and compared with the treatment plan. We also investigated daytime volatility during the treatment period. The mean bladder volume ultrasonography mean (BV_{USmean}) was found to be 302 ± 89 ml (range: 168 ± 166 ml) –553 ml). BV_{USmean} was 84 % of BV_{CTmean}. Ultrasound-measured bladder volume was smaller than that measured by CT. The correlation coefficient between BV_{USmean} and BV_{CTmean} was 0.187 (p = 0.322). Bland-Altman analysis showed that the BV_{CTmean} and BV_{USmean} agreement ranged from –202.17 to 315.83, with an average value of 70. The mean (bias, bias) and standard deviation (precision) of the differences between the two measurements was 56.83 ± 132.14 ml. BV_{CTmean} and BV_{USmean} showed a large range of change. $BV_{USWeekly1-5}$, which was measured Weeklyly, showed a certain decrease with the treatment time, as compared with BV_{CTmean}. In conclusion, large changes and differences in bladder volume should always be treated with ultrasound before treatment, and the range of rectal area should coincide. Therefore, excessive radiography is unnecessary.

Keywords : proton beam in magnetic field, Planning Target Volume (PTV) margin, rectal balloon, BV_{CTmean}, BV_{USmean}

1. Introduction

Prostate cancer is the second most common cancer in men worldwide, and its incidence is more than doubled when prostate cancer is detected early in the prostate-specific antigen test (PSA). In the early stage of cancer, radiotherapy is performed in many cases, and the prostate moves according to the state of the surrounding bladder and rectum. Although prostate movement in past research has varied depending on the research data, Langen et al. have reported that the prostate movement is about 5 mm, and the movement is up to 20 mm [1]. These changes are now being reduced by pretreatment of normal organs around the prostate. In general, three-dimensional conformational radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) is performed, compared with conventional radiotherapy (CRT). Proton therapy, which is a particle radiation therapy, is now widely used. The development of treatment planning for radical prostatectomy for localized prostate cancer can significantly reduce the incidence of rectal complications, which can safely scan over 70 Gy of radiation, but it has difficulties with urinary tract adverse effects [2-4]. In addition, the 70 Gy study suggests that 50 % of patients with moderate to severe urinary incontinence, urinary retention, rectal bleeding, and other complaints may experience a low level of acute urinary tract adverse events during the 6-7 Weekly treat-

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ment period. Acute urinary tract adverse events are also predictors of the occurrence of chronic urinary tract adverse events [5, 6]. Therefore to reduce side effects, it is necessary to fill the bladder, and reduce the area of the bladder contained in the irradiation field. However, if the volume of the bladder does not become constant, the prostate cannot receive a sufficient amount of dose, due to the change in the position of the prostate. On the other hand, if the bladder is emptied, the movement of the prostate position is reduced, and accurate dose calculation is possible. For these reasons, it is more effective in most prostate cancer treatments to fill the bladder, and administer radiation therapy [7, 8]. Recently, one of the most important factors affecting treatment efficacy and adverse effects in IMRT and proton therapy is tumor location reproducibility and patient treatment posture accuracy. IMRT is a very precise method of treating the dose distribution, by dividing each radiation field into several small beamlets. On the other hand, unlike conventional radiotherapy, proton therapy has the physical properties of the Bragg peak due to particle radiation and rapidly emits radiation after the peak. Therefore, the amount of radiation can be greatly reduced because almost no radiation is irradiated to the normal tissue around the cancer tissue. In particular, in both more precise and recent treatments, and the precise pretreatment of the prostate cancer, therapeutic centering through imaging and the absence of tumor movement are important. In prostate radiation therapy, the accuracy of volume measurement of the bladder is important in assessing treatment outcome after radiation therapy, and is crucial in assessing side effects. Therefore, in this study we investigate with accurate statistical values the volume change of the bladder that can cause prostate movement during the radiation treatment of prostate cancer, and consider the accurate PTV margin in treatment plan based on the result.

2. Study Subjects and Methods

2.1. Study subjects

Thirty patients with prostate cancer who received proton therapy from March to October 2016 were included. The patients were T1cN0M0 3, T2aN0M0 19, T3aN0M0 6, and T3bN1M0 2. The age of the patients was 51 to 77 years (mean 65 ± 15 years).

2.2. Study method

Before proton therapy, three gold fiducial markers (19.3 g/cm^3) were fixed on the prostate by ultrasonography to confirm the exact prostate location on X-ray. Marker location selects the prostate tumor site where treatment plan DRR reconstruction and DIPS imaging can appear without overlapping the three points. First, the urine was completely emptied 2 hours before the CT-Simulation, and urine was not detected by ultrasonography. Next, an enema was performed to completely remove feces and gas from the rectum, and 500 cc of water was orally ingested for 1 hour and 30 minutes to fill the bladder. Before the CT scan, a bladder scan was used to measure the volume before taking the bladder. The mean value was recorded as the Bladder volume. The Scan Probe was calibrated at a Superior 30° angle from the top of the Pubic symphysis to the Bladder, and the measurement point was displayed on the patient's skin. The bladder scan was taken by a physician, and measured by one observer. The patient’s posture was constrained by minimizing the patient’s movements in a comfortable lying posture, and the Med-Tec Dual Leg Locker mechanism was used for the patient’s leg fixation reproducibility at

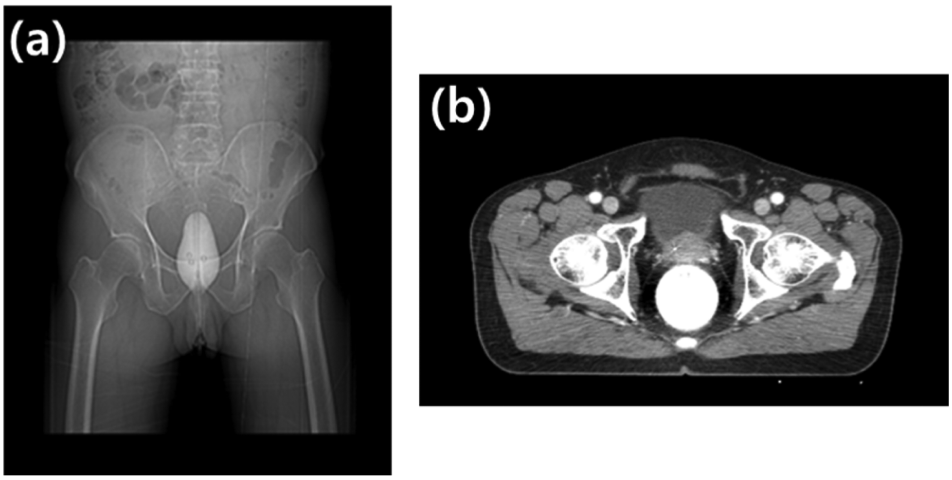

Fig. 1. CT scan axial image (A), and CT scan AP scout image (B).

each treatment. A CT scan (light speed 5.X, GE, USA) for treatment planning was performed at 2.5 mm intervals from 3 cm above the iliac crest to 5 cm below the pubic symphysis (Fig. 1). The planned CT images were acquired using the Eclipse Proton Dose Calculation Algorithm (Version 10.0.28, Varian, USA). Contouring was performed with the right femoral head, left femoral head, bladder, rectum, planning target volume (PTV), Body, and PTV to

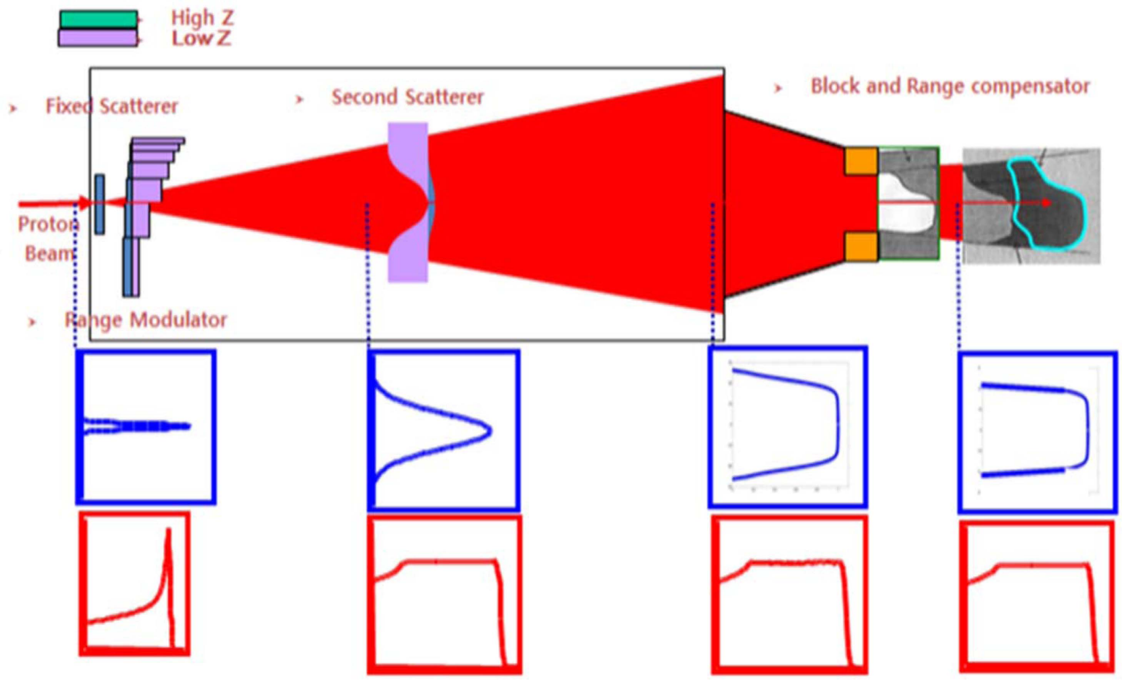

Fig. 2. (Color online) In the passive mode used for prostatic cancer treatment in proton therapy, the double scattering mode scheme.

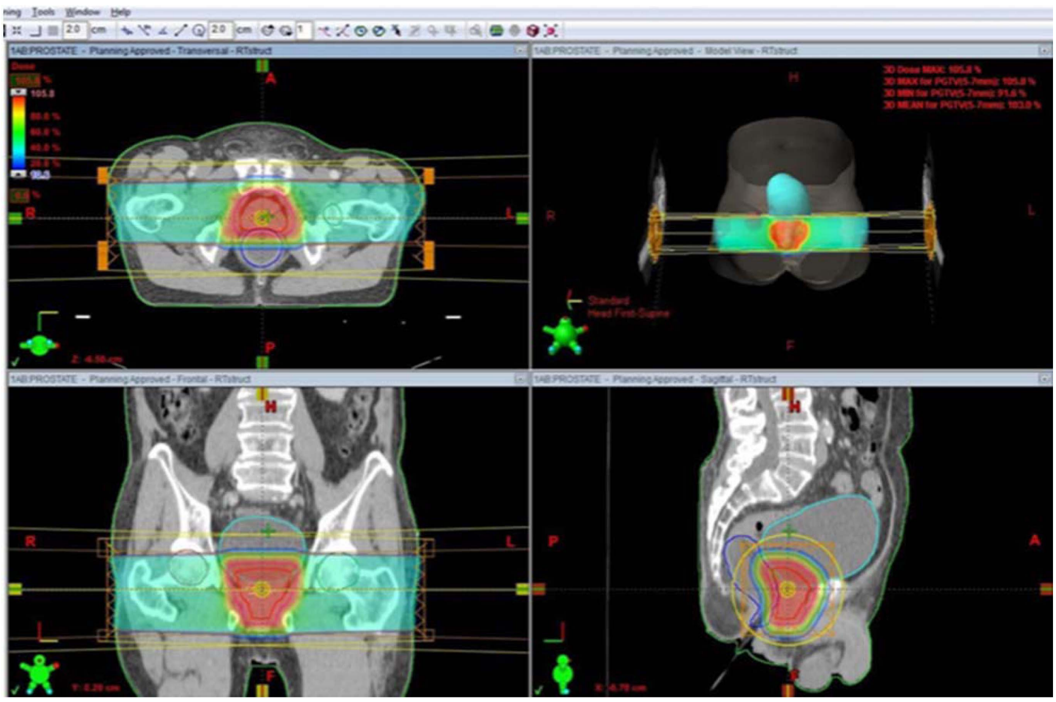

Fig. 3. (Color online) Beam orientation and dose distribution image after proton therapy plan image (red: Planning target volume, blue: Proton beam)

give a 7 mm margin in gross tumor volume (GTV). The proton beam delivery uses a passive mode double scattering mode, range compensator for tumor shape and depth, and aperture block for normal occlusion. There are two passive mode and dynamic mode of output beam used for proton therapy. The passive mode is divided into two types of double scattering mode and single scattering mode. Dynamic mode is classified into two types of uniform scanning mode and pencil beam scanning mode. The double scattering mode method used in the passive mode is a proton beam. In the first scatterer, the SOBP of the desired length is generated in the Rage modulator, and the optimal dose distribution defining the depth and shielding can be created using the compensator and block (Fig. 2). In the treatment planning, the proton beam's distal and proximal margins are 2 mm, the aperture margin is 10 mm, the smoothing of the compensator is 10 mm, and the proton beam is the proton stopping power curve in Hounsfield units (HU). Smearing was 3 mm. The air gap of Snout was set to 2 cm. The dose calculation grid size was 2.5 mm, and the beam weighting was equal to the prostate 1:1 ratio. The prescription dose amounted to 70 Gy in 95 % of PTV over 28 times of 2.5 Gy per day. The Beam Angle was a two-door survey of the right and left directions (Fig. 3). On the first day of treatment with proton therapy in the bladder volume measurement, the patient underwent the same pretreatment as in the CT-simulation, and was measured by bladder scan at the same position indicated to the patient (Fig. 4). The bladder volume computed tomography mean (BV_{CTmean}) measured by treatment plan and bladder volume ultrasonography mean (BV_{USmean}) measured by ultrasound 25 times daily were obtained for each of the 30 patients. BV_{CTmean} and BV_{USmean} values were compared using the SPSS (version 20.0, IBM, Chicago) statistical program. Bladder volume was calculated by comparing BV_{CTmean} with $BV_{USWeekly1\text{-}5}$. The bladder volume was calculated as the change in time during the treatment period. The bladder volume (BV_{CTmean}) and the Weeklyly bladder volume ($BV_{USWeekly1}$, $BV_{USWeekly2}$, … $BV_{USWeekly5}$). We also investigated Weeklyly volatility indicating a certain pattern. One-sample t test and Pearson's correlation coefficient were used for statistical analysis using BV_{CTmean} and BV_{USmean}, SPSS (version 20.0, IBM, Chicago). A P value of less than 0.05 was considered statistically significant. Bland-Altman Plot analysis was performed for the comparison of measured values.

3. Results

3.1. Comparison of BV_{CTmean} and BV_{USmean} measurements

BV_{CTmean} and BV_{USmean} were measured at the correct time 1 hour and 30 minutes after oral administration of 500 cc of water after urine and enema. BV_{CTmean} was 359 ± 116 ml (range 200-600 ml) and BV_{USmean} was 302 ± 89 ml (range 168-553 ml) (Table 1). BV_{USmean} was 84 % of BV_{CTmean}. Ultrasound-measured bladder volume was smaller than the bladder volume measured by CT. The correlation coefficient between them was 0.187, showing a statistically weak positive correlation ($p = 0.322$) (Table

Table 1. One-Sample T test of BV_{CTmean} and BV_{USmean} (unit: ml).

	Average	Standard Deviation
BV_{CTmean}	358.93	115.72
BV_{USmean}	302.27	89.11

Table 2. Pearson's correlation coefficient of BV_{CTmean} and BV_{USmean}.

	BV_{CTmean}	BV_{USmean}
BV_{CTmean}	1.00	0.187
BV_{USmean}	0.187	1.00
P	0.322	

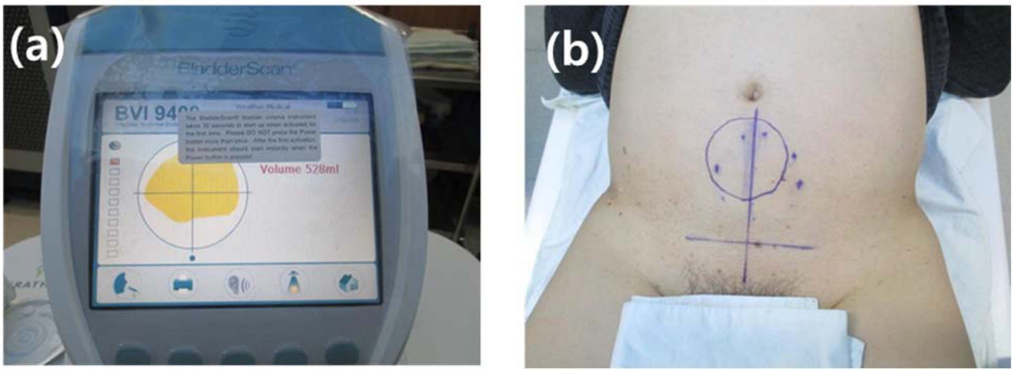

Fig. 4. (Color online) Bladder volume measurement point patient skin display (A), and bladder volume measurement result (B).

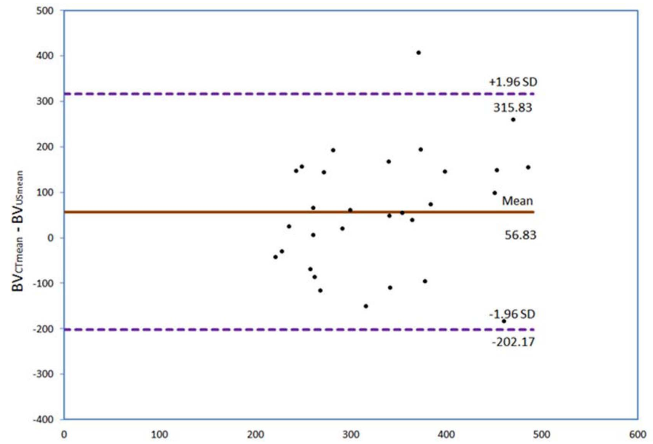

Fig. 5. (Color online) Bland-Altman analysis results of $BV_{CT\text{-}mean}$ and BV_{USmean}.

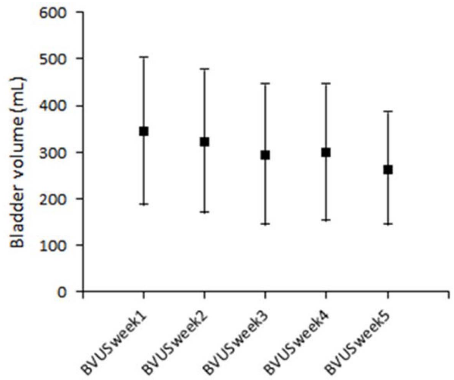

Fig. 6. Bladder volume during the 30-year radiotherapy period Weeklyly fluctuation value, where y-axis shows the value measured with ultrasound and standard deviation.

2). Bland-Altman analysis was performed. The BV_{CTmean}–BV_{USmean} agreement ranged from –202.17 to 315.83, with an average value of 70. The mean and standard deviation of the differences between the two measurements was 56.83 ± 132.14 ml. As a result, the bladder area and the pre-treatment ultrasonic bladder area differed in the CT imaging plan (Fig. 5).

3.2. Weeklyly volatility of bladder volume

BV_{CTmean} was 359 ± 116 ml (range 200-600 ml). $BV_{WKmean1}$ (1-5 day) was measured at 344 ± 18 ml, and was less than BV_{CTmean} ($p < 0.05$). $BV_{WKmean2}$ (6-10 days) at 2 Weeklys was measured at 322 ± 25 ml, and was less than BV_{CTmean} ($p < 0.05$). $BV_{WKmean3}$ (11-15 days) at 3 Weeklys was measured at 295 ± 9 ml, and was less than BV_{CTmean} ($p < 0.05$). 4 $BV_{WKmean4}$ (16-20 days) was measured at 298 ± 23 ml, and was less than BV_{CTmean} ($p < 0.05$). $BV_{WKmean5}$ (21-25 days) at 5 Weeklys was measured at 264 ± 21 ml, and was less than BV_{CTmean} ($p < 0.05$). The changes in bladder volume with time during the treatment period showed a definite decrease (Table 3) (Fig. 6).

4. Discussion

The use of ultrasound to measure bladder volume in patients with prostate cancer has been widely used as a simple and noninvasive method [9, 10]. Khurshid R. Ghani *et al.* [11] conducted a series of bladder scans of 50 patients with no bladder volume in the study. The results were compared with those of Bladder Scan. The coefficient was 0.98 ($P < 0.001$), which is very accurate, compared to other equipment. Therefore, the bladder scan accuracy was found by itself in this study. In the Lee et al. [12] study, 55 % of the bladder volume measured by ultrasonography compared to other studies was 55 % of the bladder volume measured by CT. Ultrasonography was performed after an average of 56 minutes of drinking water, and an average of 69 minutes The bladder volume between them was increased.

However, in this paper, the change of bladder volume was not significant compared with the previous paper, because CT scan and ultrasonography were performed at 1 hour and 30 minutes after drinking water. Therefore, it is very important to make the measurement time of the CT scan the same as that of the Bladder Volume. However, this study did not maintain a constant bladder volume during the radiation therapy period, which took place 1 hour and 30 minutes after emptying the bladder, and drinking 500 ml of water. In previous studies, the bladder filling and radiation treatment resulted in variance in bladder volume [13, 15]. The most common cause of bladder volume inconsistency is that many factors determine urinary volume besides water intake. Yeung *et al.* [16] reported that urine volume is influenced by hormone,

Table 3. Comparison of bladder volume computed tomography mean (BV_{CTmean}) and Weeklyly bladder volume $BV_{USWeekly1\text{-}5}$.

(unit: ml)

Measurement method	Weekly 1	Weekly 2	Weekly 3	Weekly 4	Weekly 5
BV_{CTmean}			358.93		
BV_{USmean}	344.05	322.47	294.98	298.45	263.99

age, degree of dehydration, blood pressure, patient activity, ambient temperature (temperature and altitude), and functional bladder capacity.

In our study, these factors were thought to be different for each patient. In addition, although there was sufficient knowledge about the pre-treatment, there were cases in which the difference value was large when each patient's efforts were insufficient. The bladder volume measurement result of BV_{CT} and BV_{US} showed a difference of 16 % in the bladder volume measurement result. In the daytime variability result, the ultrasonic bladder volume gradually decreased with the treatment time, and 73 % of the results were spoiled. In the study of Maria *et al*. [17], the volatility of the bladder wall and the function of the genitourinary tract were reduced during radiation therapy. In addition, according to other study [18-20], acute chronic urinary tract adverse effects increase with increasing bladder volume receiving more than 30 % of prescription dose. Therefore, in this paper, accurate measurement statistics of Bladder Volume during treatment period can be said to be the most important factor, in terms of the occurrence of side effects.

5. Conclusion

In this study, pretreatment of bladder was performed before and during treatment. Statistical analysis of bladder fluctuation value is important in predicting adverse effects in the future. In conclusion, we suggest that ultrasound should always be used for precise measurement before treatment, for large changes and differences in bladder volume.

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Sun-Yung Kim and Hae-Kag Lee equally contributed to this work. They are co-authors of first.

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