Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Investigation of the changes in the prostate, bladder, and rectal wall sizes during external beam radiotherapy

Osamu Tanaka[a,*], *Kensaku Seike*[b], *Takuya Taniguchi*[a], *Kousei Ono*[a], *Masayuki Matsuo*[c]

[a] *Asahi University Hospital, Department of Radiation Oncology, Japan*
[b] *Gifu Municipal Hospital, Department of Urology, Japan*
[c] *Gifu University, School of Medicine, Department of Radiology, Japan*

ARTICLE INFO

Article history:
Received 13 December 2017
Received in revised form
5 December 2018
Accepted 7 February 2019
Available online 22 February 2019

Keywords:
Radiotherapy
Prostate
Size change
MRI

ABSTRACT

Aim and background: The change in the prostate size for radiotherapy has not yet been elucidated. The coverage of radiation dose is affected by changes in the prostate size. We evaluated the changes in the prostate, rectum, and bladder wall sizes during IMRT of fraction 2 Gy/day using MRI.

Materials and methods: Twenty-four patients with prostate cancer were enrolled in this study. MRI was performed at three time points. While the initial MRI was performed before the start of radiotherapy (RT), the second MRI was performed at 38 Gy (range: 36–40 Gy), which represented the halfway point of the RT course. The last MRI was performed on the day of completion of the RT course (76 Gy; range: 74–78 Gy). We estimated the prostate, rectum, and bladder wall sizes at three time points.

Results: We observed no significant difference between the estimated sizes of the prostate during RT in all three phases. In addition, the volume of the rectal wall remained unchanged in all phases. However, the volume of the bladder wall significantly decreased from the initial to the last time points. Furthermore, the standard deviation (SD) obtained by subtracting the final size from the initial one was large (mean, 30.1; SD, 10.1).

Conclusions: The volume of the bladder wall decreased during IMRT. The range of subtraction of the volume of the bladder wall was extensive. Thus, the estimation of the bladder wall may be useful to reduce the inter-fraction variation.

* *Corresponding author at*: 7-1 Kashima-cho, Gifu 500-8513, Japan.
E-mail address: c.bluered@gmail.com (O. Tanaka).

https://doi.org/10.1016/j.rpor.2019.02.005

1. Background

Intensity-modulated radiotherapy (IMRT) is an extensively used treatment modality for prostate cancer, which helps deliver the prescribed dose to the target volume with minimal radiation exposure of the organs at risk (OAR).[1] When the prostate size changes during radiotherapy (RT), an irradiated area of the target changes. Therefore, it is important to evaluate the volume of the prostate, bladder, and rectal wall during the treatment. Although we recognized the position of the prostate using two markers, we could not estimate the change in size during RT even if the marker was used.

2. Aim

We measured the change in the volume of the prostate, rectum, and bladder during RT by magnetic resonance imaging (MRI), and not cone-beam computed tomography (CT).

3. Materials and methods

In this study, 24 consecutive patients with prostate cancer who were treated with IMRT at our hospital between September 2015 and March 2016 were enrolled. This study was approved by the Institutional Review Board and registered in the University Medical Network Clinical Trial Registry. All the patients provided written informed consent to participate in this study. All the patients were histopathologically diagnosed with prostate adenocarcinoma, and risk classification was performed according to the D'Amico classification. None of the patients received hormonal treatment (neoadjuvant therapy) either before or during RT. Adjuvant treatment was administered to high-risk patients, after the completion of RT, at the Urology Department of our hospital.

Patients in the low-risk, intermediate-risk, and high-risk groups were administered total radiation doses of 74, 76, and 78 Gy, respectively. Of note, patients with lymph node or distant metastases were excluded from this study. The treatment was planned according to the Eclipse Treatment Planning System (Varian Medical Systems, Inc., Salt Lake City, UT, USA).

The target volume and OAR were defined according to the International Commission of Radiation Units and Measurements. The gross target volume (GTV) includes the prostate and 2-cm proximal of the seminal vesicles, which is within 2 cm from the root of the prostate. While the clinical target volume (CTV) is a 5-mm margin from GTV, the planning target volume (PTV) is a 5-mm margin from CTV. We contoured the rectum and bladder by primarily using CT. Both the rectal and bladder walls had a 4-mm internal margin from the rectal and bladder surfaces, respectively. In this study, all the prostate volumes were measured by one radiation oncologist.

Regarding planning, the prescribed dose of 74–78 Gy to PTV covers 95% of PTV and D_{max} is 110% of the prescription dose. The prescribed dose for PTV was 74–78 Gy; 2% volume of the rectal wall was not more than 78 Gy, 25% of 70 Gy, 35% of 60 Gy, and 60% of 40 Gy. Regarding the bladder, 5% volume was not more than 78 Gy and 55% of 40 Gy; the plan normalization was 100% and covered 95% of PTV. We made a 100% replan that covered 95% of PTV, same as the initial plan. We considered the dosage of the rectal wall the most in the planning, and we examined whether the dosage of OAR fitted within the same initial plan regulation. We used five gantry angles of 45°, 105°, 180°, 255°, and 315° and 10 MV energy.

Although CT-defined prostate segmentation is mandatory according to the study protocol, MRI is recommended to target delineation. We placed two gold fiducial markers (Gold Anchor; Naslund Medical AB Vassvagen, Huddinge, Sweden) in the prostate 3 weeks before planning a CT/MRI examination. The markers were well visualized on a cone-beam CT scan using the Novalis Tx System (Varian Medical Systems, Inc., Palo Alto, CA). We matched the cone-beam CT scan with the planned CT-guided scan with markers.

3.1. *Image acquisitions*

All the patients drank 200 mL of water 30 min before CT and MRI examinations to accumulate urine in the bladder to some extent. Then, we performed external-beam planning CT (Optima CT580; GE Medical Systems, Milwaukee, WI) and MRI (Intera 1.5 Nova; Philips Medical Systems, Eindhoven, the Netherlands). The MRI scan was performed within 20 min after the CT scan using a five-channel sense cardiac coil (3-mm section thickness with no intersection gap and a 16-cm field of view). The approximate scan time for the sequence was 6–7 min.

We used T2*-weighted spin-echo [repetition time (TR)/echo time (TE) in milliseconds; range, 700/18], and the average number of signals was four. The numbers of phase-encoding and frequency-encoding steps were 205 and 256, respectively, with typical spatial resolutions. In addition, frequency/phase was 0.63/0.78. Contouring of the prostate and OAR was performed by a radiation oncologist with 20 years of experience with RT.

MRI was performed at three time points. While the initial MRI was performed 3 days before the start of RT, the second imaging was performed at 38 Gy (range: 36–40 Gy), which represented the halfway point of the RT course. The last MRI was performed at the completion of the RT course (76 Gy; range, 74–78 Gy). We assessed the bladder and rectal wall volumes along with the prostate. Differences in the prostate volume were assessed at three time points for statistical significance using a standard two-sided *t*-test. We considered $P < 0.05$ as statistically significant.

4. Results

No significant difference was observed between the estimated sizes of the prostate during RT in all three phases (Table 1). Fig. 1 shows an example of MRI, and Table 2 shows that the size of the bladder wall decreased from pre-RT to mid-RT.

Table 1a – Mean prostate volume at the three time points: pre-radiotherapy (pre-RT), mid-RT, and post-RT.

	Pre-RT	Mid-RT	Post-RT
Mean prostate volume (cm^3)	38	36.9	38.3
SD (cm^3)	17.4	20	19.2

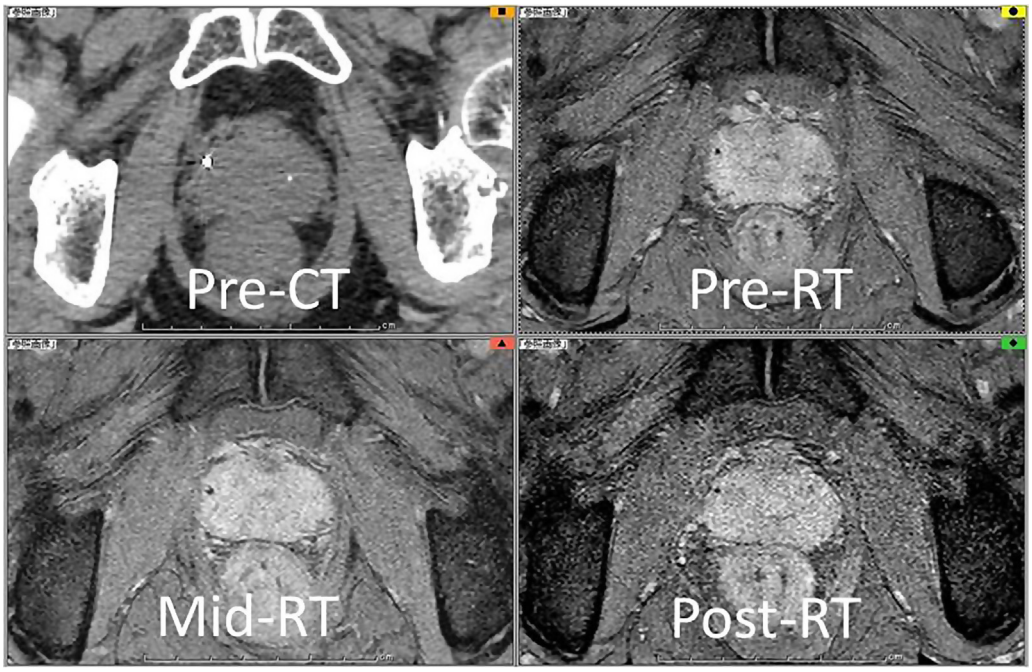

Fig. 1 – Example of the time course of the prostate volume change. *Abbreviations*: Pre-CT, pre-radiotherapy computed tomography; Pre-RT, baseline magnetic resonance imaging (MRI); Mid-RT, MRI at the mid-point of the radiotherapy course (about 38 Gy); Post-RT, MRI at the completion of the radiotherapy course.

Table 1b – Mean subtraction of prostate volumes at the three time points: pre-radiotherapy (pre-RT), mid-RT, and post-RT.

	Pre–Mid	Mid–Post	Pre–Post
Subtract (cm^3)	1.2	1.2	3.4
SD (cm^3)	7.1	7.4	5.9
P	0.44	0.59	0.08

Abbreviations: SD, standard deviation; Pre-RT, pre-radiotherapy; Mid-RT, median time to perform MRI and CT examinations (36 Gy; range, 34–38 Gy); Post-RT, at the completion of radiotherapy (total dose: 74–78 Gy).

Table 2a – Mean bladder and rectal volumes at the three study time points: pre-radiotherapy (pre-RT), mid-RT, and post-RT.

	Pre-RT	Mid-RT	Post-RT
Mean bladder wall volume (cm^3)	67.2	55.4	57.6
SD (cm^3)	21.4	27.6	25.1
Mean rectal wall volume (cm^3)	28.3	27.5	26.1
SD (cm^3)	4.2	3.8	3.7

The rectal wall did not change throughout the treatment. The mean pre-RT prostate size in our study was 38.0 cm^3; the prostate size at the mid-point of the RT course was 36.9 cm^3, and the final size was 38.3 cm^3. Furthermore, the subtracted value of the prostate volume at the three points did not vary significantly.

Table 2b – Mean subtraction of bladder and rectal wall volumes at the three time points: pre-radiotherapy (pre-RT), mid-RT, and post-RT.

	Pre–Mid	Mid–Post	Pre–Post
Bladder wall			
Subtract (cm^3)	21.3	8.2	30.1
SD (cm^3)	10.4	6.1	10.1
P	<0.01	0.12	<0.01
Rectal wall			
Subtract (cm^3)	2.3	3.4	5.7
SD (cm^3)	3.7	3.9	2.4
P	0.45	0.38	0.74

5. Discussion

To date, few studies have evaluated the prostate size during treatment. Gunnlaugsson et al. reported a significant increase in the mean prostate volume (14%) at the mid-point of the RT course compared with that at baseline. The increase in the mean prostate volume tended to persist during the RT course; the mean prostate volume at the completion of RT was 9% higher than that at baseline. In fact, the increase in the prostate volume was most pronounced in the anterior–posterior and craniocaudal axes.[2,3] However, because their analysis was derived from hypofractionated (7 × 6.1 Gy) RT for prostate cancer, it does not corroborate with our results because our study was conducted using IMRT of fraction 2 Gy/day (total, 37–39 fractions). Kim et al. reviewed the published MEDLINE literature regarding the surgical feasibility of prostatectomy in the Asian population and found that most Asians still had a shorter stature, a lower BMI, and smaller

prostates.[4] Their results are similar to our background of the prostate size. If the prostate size changed during RT, the target volume also changed. Although some studies have investigated prostate size, their reports were an evaluation of pre-RT and post-RT.[5–9]

In general, changes in the target volume changed GTV, VTV, and PTV. However, the background of the prostate size varies between Western and Asian populations. Pinkawa et al. reported that patients with larger prostates (59 cm^3) were at a higher risk of irritative symptoms (particularly dysuria) in the acute RT phase than those with small prostates (31 cm^3).[5] In addition, they compared the rectal and bladder doses using a dose-volume histogram. During treatment, inflammation and atrophy may cause prostate enlargement, shrinkage, or both at different phases. These studies have highlighted an overall prostate volume reduction at the end of the treatment (in the absence of any anti-hormonal treatment), although an initial increase in volume was observed.[9] They concluded that dose coverage affected the change in the prostate size and thus recommended consideration of this while determining the CTV and PTV margins. Conversely, Deurloo et al. contoured the prostate on weekly CT scans during RT but observed no change in volume. However, their estimation of the prostate size was based only on CT scans.[7]

Sanguineti et al. reported a 15% reduction in the mean prostate size during the RT course when planning CT was performed within 3 months from neoadjuvant androgen-deprivation therapy.[8] Gunnlaugsson et al. determined that extreme hypofractionation induced a significant prostate swelling during treatment.[2] In this study, we used 2 Gy/day; the discrepancy between our results and those of previous studies could be attributed to the edema ratio because of the number of fractions and the amount of dosage in one fraction.

However, this study has some limitations. First, the number of patients enrolled in this study was very low. Second, the prostate size did not change with a dosage of 2 Gy/day. Cone-beam CT has been found to be unreliable for the precise estimation of the prostate. Although the fiducial markers were matched on planning CT and CBCT, whether the prostate size was the same as the initial size remains controversial. If the size varies during RT, we should consider MRI and CT while replanning. Finally, the prostate size of every patient did not vary significantly in our small study population.

DVHs are affected not only by the prostate size but also by the motion of the inter-fraction variation. Because the prostate size did not change during the treatment, we fused the position of the prostate using fiducial markers on planning CT and cone-beam CT. However, the bladder wall size should be considered carefully because when the bladder is moved superior, the prostate may also move superior. In this study, we made a replan for all cases; however, we did not mention the adaptive plan (using second MRI and CT set) because it is subjective and the inter-physicist variation may be large, we did not include DVH analysis.

6. Conclusions

In this study, no significant change was observed in the prostate and rectal wall sizes during IMRT. However, the bladder wall size decreased during the RT course. In addition, the range of subtraction of the bladder wall volume was considerable. Thus, this study suggests that the estimation of the bladder wall may be useful in reducing the inter-fraction variation, and it is not necessary to reevaluate the prostate size during RT in a small-volume prostate.

Registered National Clinical Trial Systems

All patients provided written informed consent.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Troeller A, Yan D, Marina O, et al. Comparison and limitations of DVH-based NTCP models derived from 3D-CRT and IMRT data for prediction of gastrointestinal toxicities in prostate cancer patients by using propensity score matched pair analysis. *Int J Radiat Oncol Biol Phys* 2015;**91**:435–43.
2. Gunnlaugsson A, Kjellén E, Hagberg O, Thellenberg-Karlsson C, Widmark A, Nilsson P. Change in prostate volume during extreme hypo-fractionation analysed with MRI. *Radiat Oncol* 2014;**13**:22.
3. Tanaka O, Hayashi S, Matsuo M, et al. MRI-based preplanning in low-dose-rate prostate brachytherapy. *Radiother Oncol* 2008;**88**:115–20.
4. Kim MJ, Park SY, Rha KH. Influence of prostate weight, obesity and height on surgical outcomes of robot-assisted laparoscopic radical prostatectomy in Korean men. *J Robot Surg* 2008;**4**:287–90.
5. Pinkawa M, Fischedick K, Asadpour B, et al. Toxicity profile with a large prostate volume after external beam radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:83–9.
6. Zellars RC, Roberson PL, Strawderman M, et al. Prostate position late in the course of external-beam therapy: patterns and predictors. *Int J Radiat Oncol Biol Phys* 2000;**47**:655–60.
7. Deurloo KE, Steenbakkers RJ, Zijp LJ, et al. Quantification of shape variation of prostate and seminal vesicles during external-beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;**61**:228–38.
8. Sanguineti G, Marcenaro M, Franzone P, Foppiano F, Vitale V. Neoadjuvant androgen deprivation and prostate gland shrinkage during conformal radiotherapy. *Radiother Oncol* 2003;**66**:151–7.
9. King BL, Butler WM, Merrick GS, et al. Electromagnetic transponders indicate prostate size increase followed by decrease during the course of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;**79**:1350–7.