

Usefulness of CT-MRI Fusion in Radiotherapy Planning for Localized Prostate Cancer

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Prostate cancer/Radiotherapy/CT-MRI fusion.

We compared the prostate volumes and rectal doses calculated by CT and CT-MRI fusion, and verified the usefulness of CT-MRI fusion in three-dimensional (3D) radiotherapy planning for localized prostate cancer. Three observers contoured the prostate and rectum of 13 patients with CT and CT-MRI fusion. Prostate delineations were classified into three sub-parts, and the volumes and distances to the rectum (PR distance) were calculated. 3D radiotherapy plans were generated. A dose-volume histogram (DVH) was constructed for the rectum. The intermodality and interobserver variations were assessed. CT-MRI fusion yielded a significantly lower prostate volume by 31%. In the sub-part analysis, the greatest difference was seen for the apical side. The PR distance was significantly extended by 3.5-mm, and the greatest difference was seen for the basal side. The irradiated rectal volume was reduced in the CT-MRI fusion-based plan. The reduction rates were greater in the relatively high-dose regions. The decrease of the prostate volume and length alteration of the distance between the prostate and rectum were correlated with the decrease of the irradiated rectal volume. The prostate volume delineated by CT-MRI fusion was negatively correlated with the decrease of the irradiated rectal volume. CT showed a tendency towards overestimation of the prostate volume and underestimation of the PR distance as compared to CT-MRI fusion. The rectal dose was significantly reduced in CT-MRI fusion-based plan. Using CT-MRI fusion, especially in cases with a small prostate, the irradiated rectal volume can be reduced, with consequent reduction in rectal complications.

INTRODUCTION

In recent years, brachytherapy with permanent seeds and external beam radiotherapy, such as intensity-modulated radiotherapy and three-dimensional (3D) conformal radiotherapy, have been employed in many institutions for the treatment of localized prostate cancer as an alternative to radical prostatectomy.¹⁾ At present, computed tomography (CT) -based delineation is the most common method for prostate contouring. Prostate is surrounded by several soft-tissue structures (bladder, seminal vesicles, venous plexus, neurovascular bundles, muscles, rectum, etc).^{2,3)} Because of the small differences in density, the interfaces between the prostate and these structures are ill-defined. Magnetic resonance imaging (MRI) has better soft-tissue resolution, and

shows the interfaces more clearly.^{4,5)} Wendy L *et al.* reported that the prostate volume as delineated using CT was larger than that delineating using MRI in brachytherapy postplan.⁶⁾ Polo A *et al.* also reported that the prostate volume and dosimetry were significantly different between CT and CT-MRI fusion in brachytherapy postplan.⁷⁾ It has also been reported that CT-MRI fusion is more useful for prostate delineation in external beam radiotherapy, and allows the rectal dose to be reduced.^{8–10)}

To the best of our knowledge, all of these reports have been published from the west and limited to external beam radiotherapy, and a similar examination for Asians with smaller physiques and smaller prostate glands had not yet been performed. There are few reports of examinations classifying the prostate into sub-parts.^{11,12)}

We examined the usefulness of CT-MRI fusion for external beam radiotherapy in Japanese prostate cancer patients.

MATERIALS AND METHODS

Patients and scans

Between January and August 2010, 13 consecutive patients with pathologically proven clinically localized pro-

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static adenocarcinoma were entered in this study. All the patients were treated by intensity-modulated radiotherapy (IMRT). The prescribed doses ranged from 74 to 78 Gy. The median age of the patients was 70 years (range 66–79 years) and the T-stage ranged from Stage T1c to Stage T3a. The median prostate specific antigen (PSA) level was 8.98 ng/ml (range 4.16–77.40).

All patients were positioned supine on a couch within the immobilization devices (HIP-FIX system, CIVCO Medical Solutions, Iowa, USA) and treated with Novalis Tx (Varian Medical Systems, California, USA and BrainLAB, Munich, Germany). Patients were instructed to move their bowels and empty their bladder 30 min prior to the treatment.

Each patient underwent CT in the treatment position within the immobilization devices. The CT scan performed using a CT scanner with 16 detector arrays (LightSpeed Xtra, GE Healthcare, Wisconsin, USA). Axial CT images of 2.5-mm thickness at 3-mm intervals were obtained. A field of view (FOV) of 15 cm, a 512-square matrix, and a standard reconstruction algorithm were used. No external markers or intravenous contrast material were used. Sagittal and coronal reformatting images were constructed.

MR imaging was also performed in the treatment position within the immobilization devices just after or prior to the CT. The MRI was performed on a 1.5-Tesla MR imager (Achieva Nova Dual, Philips Medical Systems, Eindhoven, the Netherlands). The images obtained were 3-mm axial and sagittal T2-weighted fast spin-echo images (repetition time [TR] 3000 ms, echo time [TE] 80 ms), 16 cm FOV, and matrix size of 224×156 (reconstruction 256) of the pelvis were obtained.

Both the CT and MR images were transported to iPLAN RT image 4.1 (Brain LAB, Munich, Germany). Both images automatically matched in three dimensions. The matches were visually checked in all directions and modified, if necessary, by one radiation oncologist.

Structure delineation

One radiation oncologist contoured the prostate of all the patients referring to all the CT and MR images. The geometric center of each delineation was provided for the prostate center in each patient.

Three other radiation oncologists participated as observers. Observer 1 had < 5 years of experience, observer 2 had > 10 years of experience and observer 3 had > 20 years of experience as radiation oncologists. The three observers contoured the prostate and the outer wall of the rectum on the CT images referring to the sagittal and coronal reformatting images. At a later date, they contoured the prostate and the outer wall of rectum on the CT-MRI fusion images referring to all the images. In total, 39 CT-based delineations (CT-Prostate, CT-Rectum) and 39 CT-MRI fusion-based delineations (fusion-Prostate, fusion-Rectum) were performed.

On all delineations, three slices including the prostate center selected by the methods described above were defined as Prostate-Mid for descriptive purposes. Three of the five slices cranial and caudad were defined as Prostate-Base and Prostate-Apex, respectively (Fig. 1). Furthermore, the distance from the posterior edge of the prostate to the anterior edge of the rectum in the midline was measured in each slice of these sub-parts. The average for each sub-part, defined as Prostate-Rectum distance (PR distance) -Base, PR distance-Mid, PR distance-Apex, respectively, was calculated (Fig. 2). The overall average was defined as PR distance-Total.

Treatment planning and dose calculations

Three-dimensional conformal radiotherapy plans were generated for each delineated prostate on iPLAN RT dose 4.1.2 (BrainLAB, Munich, Germany). A 7-field treatment plan was designed, with gantry angles of 45° , 90° , 135° , 180° , 225° , 270° , and 315° . The beam weight was evenly distributed. The energy of the beam was 10 MV. A dose of 70 Gy was prescribed for the isocenter. The prostate was assumed to be the Clinical target volume (CTV). The planning target volume (PTV) was constructed by adding a 6-mm margin in

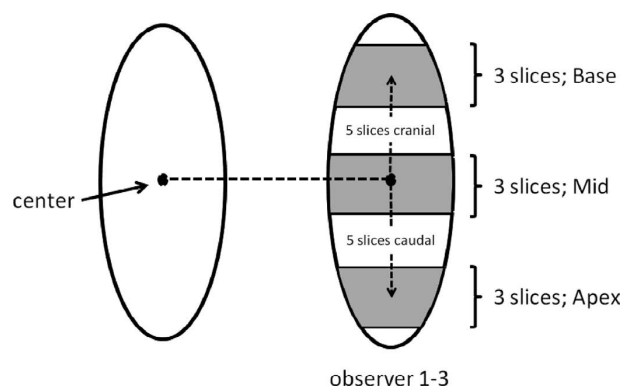


Fig. 1. Three slices including the prostate center were defined as Prostate-Mid, three of the five slices cranial and caudad were defined as the Prostate-Base and Prostate-Apex, respectively.

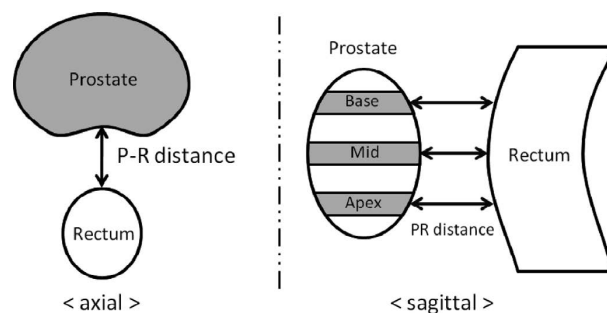


Fig. 2. The distance between the prostate and rectum in the midline was measured in each slice. The average for each sub-part, defined as Prostate-Rectum distance (PR distance) -Base, PR distance-Mid, PR distance-Apex, respectively, was calculated.

the posterior direction and a 10-mm margin in the other directions around the CTV. The leaf margin was 3 mm, with a 2.5-mm width of the multileaf collimator (MLC).

The dose-volume histogram (DVH) was constructed for the PTV and rectum. Using the DVH of the PTV, the volume of the PTV receiving at least 95% of the prescribed dose (V95%), and the mean and maximal dose (Dmean and Dmax, respectively) to the PTV were calculated. Using the DVH of the rectum, the volume of the rectum receiving at least 45 Gy, 50 Gy, 55 Gy, 60 Gy and 65 Gy (V45Gy, V50Gy, V55Gy, V60Gy and V65Gy, respectively), and the Dmean and Dmax of the rectum were also calculated.

Because of the continuous peristaltic movements, the rectum does not always have the same form. An accurate comparison of rectal doses between two plans with differently defined rectal volumes cannot be done. We calculated the dose of the CT-Rectum as the rectum at a specific point in time for not only the CT-based plan but also the CT-MRI fusion-based plan.

Statistical analysis

As the intermodality study, the volume, PR-distance, and dosimetric parameters were compared using the paired *t*-test. The interobserver study was performed using one-way analysis of variance for independent samples (ANOVA). The null-hypothesis was rejected if $p < 0.05$. The correlations were analyzed using Pearson's product moment correlation coefficient (*r*).

RESULTS

Prostate and rectal volume

The mean delineated volumes of the prostate, Prostate-Base, -Mid and -Apex in each modality (CT or CT-MRI fusion) are shown in Table 1. The fusion-Prostate volume was about 31% smaller than the CT-Prostate volume. For every sub-part as well, the fusion-Prostate volume was smaller than the CT-Prostate volume, with the greatest difference seen for the Prostate-Apex, followed by that for the Prostate-Base. All differences were statistically significant ($p < 0.05$ by paired *t*-test).

The mean volumes of the CT-Rectum and fusion-Rectum were 53.4 cc and 46.2 cc, respectively. We found no statistically significant difference between these values ($p = 0.829$ by paired *t*-test).

Prostate-Rectum distance

The PR distance-Total was 3.5-mm longer in CT-MRI fusion than in CT (Table 2). For every sub-part as well, the PR distance in CT-MRI fusion was longer than that in CT, the greatest difference being seen for the Prostate-Base, followed by that for the Prostate-Apex. All differences were statistically significant ($p < 0.05$ by paired *t*-test).

Interobserver study

We found no statistically significant intramodality interobserver differences in the prostate volumes or PR distances calculated using either CT or CT-MRI fusion (one-way ANOVA) (Table 3), indicating that any intermodality differences could not be attributed to deviant delineations by one of the observers.

PTV and rectal dose

There were no significant differences in the V95%, Dmean, or Dmax of the PTV calculated using either modality.

In Table 4, the results for the Dmean, Dmax, V45Gy, V50Gy, V55Gy, V60Gy, and V65Gy of the rectum are shown. The irradiated rectal volume was lower in the CT-MRI fusion-based plan for all dose levels. The differences in the mean irradiated volume between the CT-based plan and CT-MRI fusion-based plan were 32.4%, 35.0%, 37.4%,

Table 1. Mean volume of the prostate and its sub-parts calculated using CT and CT-MRI fusion (cc).

	CT	CT-MRI fusion	%reduction
Prostate	26.90	18.57	31.0*
-Base	4.59	3.20	30.2*
-Mid	6.71	5.07	24.4*
-Apex	3.06	1.69	44.9*

* significant at $p < 0.05$ (paired *t*-test)

Table 2. Mean distance between the prostate and rectum (PR distance) at each level calculated using CT and CT-MRI fusion (mm).

	CT	CT-MRI fusion	Length alteration
-Total	5.5	9.0	3.5*
-Base	13.5	18.8	5.3*
-Mid	1.6	3.9	2.2*
-Apex	1.5	4.5	3.0*

* significant at $p < 0.05$ (paired *t*-test)

Table 3. Intramodality interobserver differences in volumes (cc) or distances (mm) between the prostate and the rectum (PR distance) calculated using CT or CT-MRI fusion.

		Observer			p value*
		1	2	3	
Mean volume of the prostate	CT	25.4	28.0	26.7	0.63
	CT-MRI fusion	18.4	19.5	18.3	0.59
Mean PR distance-Total	CT	5.9	5.4	5.3	0.89
	CT-MRI fusion	8.6	9.8	8.4	0.41

* one-way analysis of variance for independent samples (ANOVA)

39.5%, and 44.4% for V45Gy, V50Gy, V55Gy, V60Gy, and V65Gy, respectively. All differences were statistically significant ($p < 0.05$ by paired t -test). The rates of reduction were larger in relatively high-dose regions than in low-dose regions. A representative example of DVH for the rectum is presented (Fig. 3).

Correlations

The rate of reduction of the prostate volume was correlated with the rate of decrease of the rectal dose or irradiated rectal volume (Pearson’s product moment correlation coefficients). Strong positive correlations were also seen with the Dmean, V45Gy, V50Gy, and V55Gy ($r = 0.796, 0.789, 0.814$ and 0.733 , respectively; all p -values < 0.05), and positive correlations were seen with the V60Gy and V65Gy ($r = 0.691$ and 0.659 ; all p -values < 0.05). The correlation with the Dmean is shown as a representative example in Fig. 4, while comparable results were obtained for the other parameters.

The alteration in the length of the PR distance-Total showed strong positive correlations with the rate of decrease of the Dmean, V45Gy, V50Gy, V55Gy, V60Gy and V65Gy of the rectum (Pearson’s product moment correlation coefficients $r = 0.826, 0.797, 0.826, 0.829, 0.791$ and 0.767 , respectively; all p -values < 0.05) (Fig. 4).

A strong positive correlation was also seen between the rate of reduction of the prostate volume and the alteration in the length of the PR distance-Total (Pearson’s correlation coefficient $r = 0.790$; $p < 0.05$) (Fig. 5).

The volume of the fusion-Prostate had negative correlations with the rate of reduction of the prostate volume (Pearson’s correlation coefficient $r = -0.490$; $p < 0.05$), the alteration in the length of the PR distance-Total (Pearson’s correlation coefficient $r = -0.468$; $p < 0.05$) and the rate of decrease of the rectal dose or rectum irradiated volume, respectively (Fig. 6). The negative correlations were seen in Dmean, V45Gy, V50Gy, V55Gy and V60Gy (Pearson’s cor-

Table 4. Mean Dose-Volume Histogram in CT-based planning and CT-MRI fusion-based planning for the rectum.

	CT	CT-MRI fusion	%reduction
Mean dose (Gy)	36.6	20.7	18.0*
Max dose (Gy)	69.5	68.9	1.5*
V45Gy (%)	35.3	23.7	32.4*
V50Gy (%)	27.8	17.9	35.0*
V55Gy (%)	20.8	15.1	37.4*
V60Gy (%)	17.0	9.6	39.5*
V65Gy (%)	12.4	6.3	44.4*

* significant at $p < 0.05$ (paired t -test)

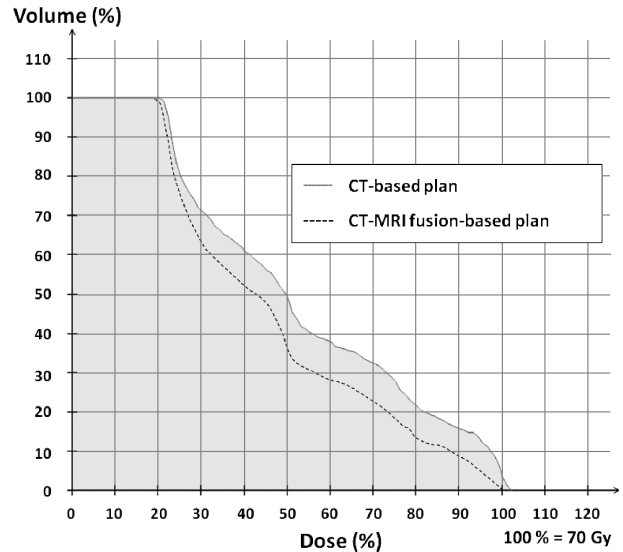


Fig. 3. The rates of reduction were larger in relatively high-dose regions than in low-dose regions. A representative example of DVH for the rectum is presented.

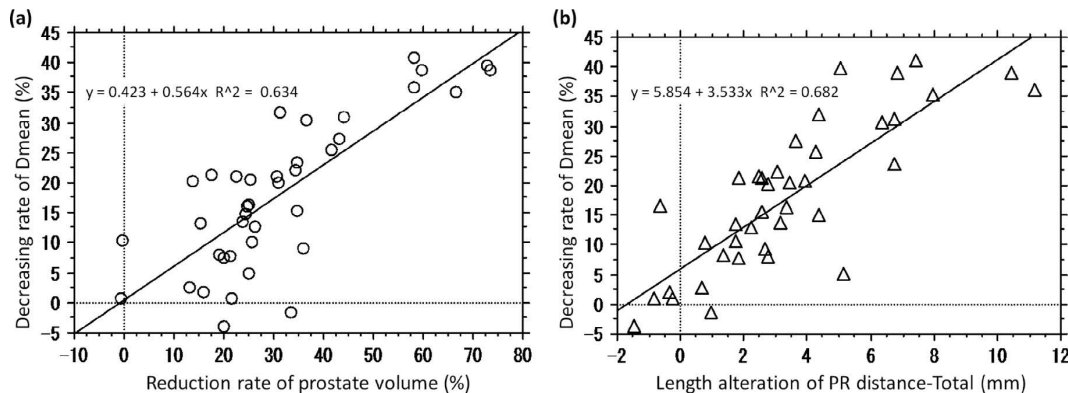


Fig. 4. The rate of reduction of the prostate volume (a) and alteration in the length of the PR distance-Total (b) showed a strong positive correlation with the rate of decrease of the Dmean. They were also correlated with the V45Gy, V50Gy, V55Gy, V60Gy, and V65Gy (not shown).

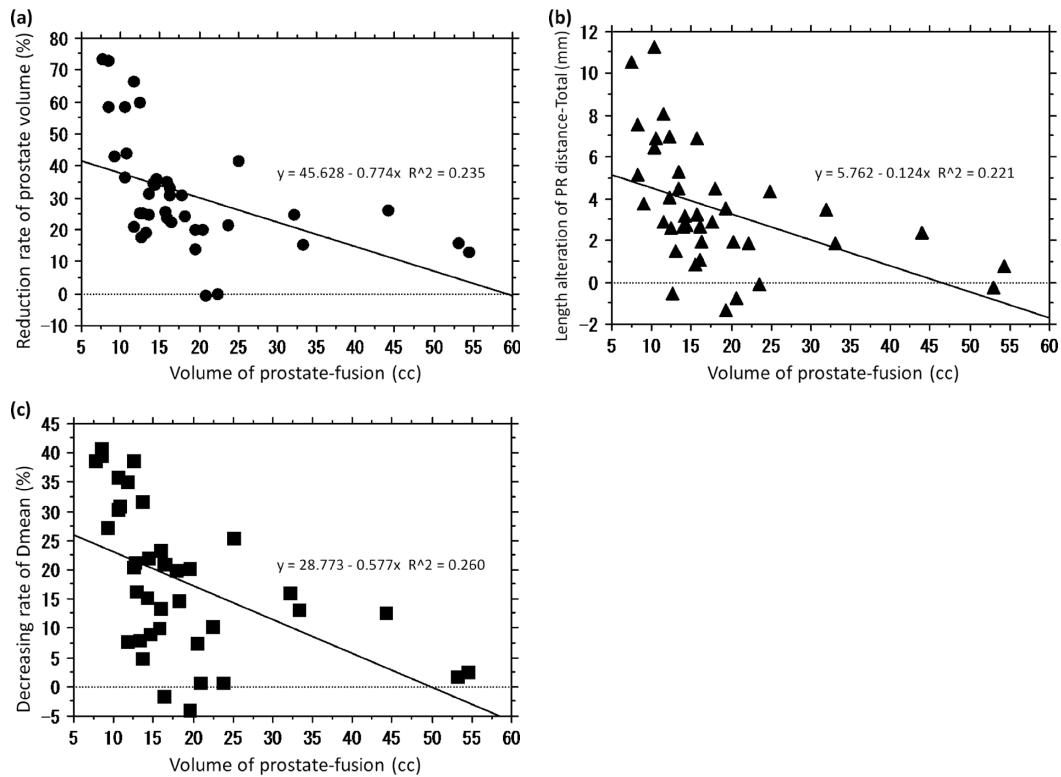


Fig. 6. The prostate volume delineated by CT-MRI fusion was negatively correlated with the rate of reduction of the prostate volume (a), the alteration in the length of the PR distance-Total (b), and the rate of decrease of Dmean (c).

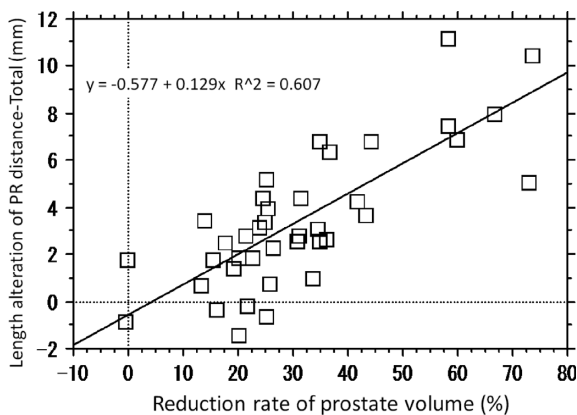


Fig. 5. The rate of reduction of the prostate volume was strongly correlated with the alteration in the length of the PR distance-Total.

relation coefficients $r = -0.510, -0.457, -0.447, -0.410$ and -0.404 ; all p values < 0.05 , respectively) and the weak negative correlation was seen in V65Gy ($r = -0.370$; $p < 0.05$). The correlation with Dmean is shown as representative example in Fig. 6.

DISCUSSION

The fuzziness of the outline of the prostate on CT tends

to result in an overestimation of the prostate volume. The risk of overestimation decreases with the use of CT-MRI fusion. Roach *et al.* reported a mean increase in the CT-acquired prostate volume by 32% as compared with that assessed on MRI in 18 patients.¹³ Debois *et al.* and Rasch *et al.* reported 45% and 43% higher volumes, respectively.^{8,14} Similarly, several authors have reported that CT-based delineation tends to result in overestimation (Table 5). In the sub-part analysis, the greatest difference was seen for the Prostate-Apex in this study. It is thought that the interface of the Prostate-Apex is ill-defined nearly-circumferentially on CT, because of the presence of several structures, such as muscles on the lateral aspect, venous plexus on the ventral aspect, and rectum on the dorsal aspect. For the same reason, the PR distance was underestimated by CT. The greatest difference was seen for the Prostate-Base. The rectum is on the dorsal side of the prostate, and the interface of the prostate with the rectum might be indistinct. At the level of the Prostate-Base, another uncertain element of the seminal vesicle exists on the dorsal side. As a result, identification of the dorsal boundary becomes further difficult.

We found no statistically significant difference between the mean volumes of the CT-Rectum and fusion-Rectum. This result does not suggest that there are no differences between CT-Rectum and fusion-Rectum. Because of the continuous peristaltic movements, the rectum does not

Table 5. Comparison of prostate volume studies using image fusion.

	No. of patients	No. of observers	Mean CT-prostate volume (cc)	Mean fusion-prostate volume (cc)	% Reduction
Roach <i>et al.</i> ¹³⁾	10	1	38.4	29.6	24.7 [†]
Rasch <i>et al.</i> ¹⁴⁾	22	1	63.0*	50.9*	21.8 [†]
Debois <i>et al.</i> ⁸⁾	18	3	63.7	44.5	30.1 [†]
Kagawa <i>et al.</i> ¹¹⁾	10	3	51.0	35.0	31.4 [†]
Sannazzari <i>et al.</i> ⁹⁾	8	1	85.8*	63.9*	25.5 [†]
This study	13	3	26.9	18.6	31.0

* : including seminal vesicles

† : converted into the reduction rate

always have the same form. The volume of the rectum is not always the same. However, when it comes to the rectum, contouring with CT, which has low contrast resolution, is not particularly difficult. Fat tissue is the only structure that can be recognized on CT or MRI images between the prostate and the rectum. When fat tissue intervenes between the prostate and the rectum, the interface of the ventral wall of the rectum is clear, because the difference in CT values between fat and the rectum is large. When fat tissue does not intervene between the prostate and the rectum, the lack of border clarity between the two is essentially due to the prostate being unclear.

Zapatero *et al.* reported that the Dmean and V60Gy were significant predictors of late rectal bleeding after 3D conformal radiotherapy for prostate cancer.¹⁵⁾ In the same context, Fiorino *et al.* and Greco *et al.* reported the importance of V50–70Gy and V60–72Gy, respectively.^{16–18)} It is assumed to be necessary to try and decrease the volume of the rectum receiving relatively high doses. In this study, the irradiated rectal volume decreased for all dose levels when CT-MRI fusion was used for the delineation. The rate of decrease increased as the dose increased. That is, the reduction rates were larger in the high-dose regions assumed to carry a higher risk of late rectal bleeding. The risk of late rectal bleeding thus decreases with the use of CT-MRI fusion for planning.

The rate of reduction of the prostate volume was correlated with the rate of decrease of the V60Gy and V65Gy, and also strongly correlated with the V45Gy, V50Gy, and V55Gy. The alteration in the length of the PR distance-Total was also strongly correlated with the rate of decrease of the irradiated rectal volume for all dose levels. Although both showed a correlation with the irradiated rectal volume, the reduction of the prostate volume originates from the borders with the ventral and lateral structures also becoming clearer, and not only that of the border with the rectum as dorsal structure, while the length alteration of the PR distance originates directly from the border with the rectum becoming clearer.

The fusion-Prostate volume was negatively correlated with the reduction rate of the prostate volume, the alteration in the length of the PR distance-Total, and the rate of decrease of the irradiated rectal volume. The smaller the prostate size, the larger these parameters are. For a patient with a small prostate due to neoadjuvant hormone therapy or a small physique, including Asians, it is suggested that CT-MRI fusion-based planning will be more useful. Hormone therapy exerts the effect of not only prostate volume reduction, but also allows a time delay to the start of treatment. Therefore, it is easy to perform MRI and create a treatment plan using CT-MRI fusion. Treatment planning with CT-MRI fusion should be actively considered for localized prostate cancer with an adequate waiting interval until radiotherapy, to reduce the possibility of late adverse events.

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