Original Knee Fixation Device as a Useful Fixation Method during Prostate Intensity-Modulated Radiation Therapy

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Purpose: The purpose of the study was to reduce setup errors during intensity-modulated radiation therapy (IMRT) with an original knee fixation device (KFD) and evaluate the clinical target volume (CTV) coverage. Methods: Participants were classified into two groups: knee flexion (KF) group \((n = 16)\), wherein participants’ knees were fixed in a flexed position using the proposed KFD during planning computed tomography, and knee extension group (KE; \(n = 15\)), wherein no KFD was used. We investigated the residual rotational errors and inter-fractional setup errors with or without KFD. Furthermore, inter-fractional margins were calculated using logistic regression analysis, and CTV coverage was evaluated. Results: The residual rotational errors in the yaw and roll directions \((P < 0.02)\) and the inter-fractional error in the anterior-posterior (A-P) direction \((P < 0.02)\) improved significantly in the KF group compared with the KE group. Repeatability was improved for the pitch direction. The inter-fractional margins were 6.68 mm and 4.87 mm in the A-P and superior-inferior (S-I) directions, respectively, in the KF group, representing reductions (mm) of 20.8% and 12.6% compared with the KE group, respectively. The odds ratios for CTV coverage in the KF group compared to the KE group were 2.76 \((P < 0.001)\) and 1.74 \((P < 0.05)\) in the A-P and S-I directions, respectively. Conclusions: The IMRT fixation method using an original KFD improved the residual rotational error in the three directions and the inter-fractional error in the A-P direction, reduced the interfractional margins in the A-P, and S-I directions and improved CTV coverage. Our original KFD may be a useful fixation method during prostate IMRT.

Keywords: Clinical target volume coverage, fixation method, intensity-modulated radiation therapy, logistic regression curve, original knee fixation device

INTRODUCTION

External radiation therapy or combined hormone and external radiation therapy is recommended for patients with moderate-to-high-risk prostate cancer.\(^{11}\) Intensity-modulated radiation therapy (IMRT) uses radiation beams whose intensity can be modulated to concentrate and mold the irradiation beam to the form of the target (tumor) from multiple directions. This therapy helps reduce the radiological dose received by the organs at risk of radiation exposure (organs at risk) while maintaining the dose received by the target in cases wherein the target and the organs at risk are in close proximity.\(^{2-5}\) However, unlike conventional irradiation methods, the accuracy with which a patient is positioned during the application of this method has a major effect on the dose received by the target and the surrounding organs at risk. Thus, it is important to maintain the accuracy of the setup.

During prostate cancer therapy, the organs at risk are the bladder and rectum because they are in close proximity, and a high degree of setup accuracy is required. However, the setup position in cone-beam computed tomography (CBCT) imaging during therapy may differ from that in computed tomography (CT) imaging owing to inadequate pretreatments.
such as bladder volume control and defecation. This is known as a setup error,\(^6\) which is classified into inter-fractional and intra-fractional setup errors. Inter-fractional setup error is affected by the volume of the bladder and rectum, whereas intra-fractional setup error is affected by an internal error, which is caused by the physiological movement of the intestinal tract. In addition to managing bladder and rectal volume, it is important to reduce the gaps between the fixation device and the body, especially for the inter-fractional setup error. Notably, maintaining the stability of the pelvic position is extremely important for reducing such gaps. Commercially available knee pillows can generally provide stability for the pelvic position and are, thus, used in conventional radiation therapy.\(^7\) In this study, a knee pillow that could be attached to the prostate IMRT fixation device was created, and a fixation method was developed to improve the stability of the pelvic position.

There are two types of image-guided radiotherapy (IGRT) methods as follows: Offline-and online-IGRT. Online-IGRT can correct inter-fractional systematic and random errors within the setup.\(^8\) In particular, online-IGRT with the 6 degree-of-freedom couch can theoretically correct inter-fractional setup errors; however, it cannot address nonlinear structural changes, such as twisting. Moreover, although online-IGRT with a 4-DoF couch is routinely performed, it does not allow the modification of the direction of rotation, especially the pitch and roll directions, and requires repeatability and stability of the position. Therefore, it is extremely important to improve positional stability to avoid nonlinear changes in the body position.

There have been several reports on the usefulness of various fixation methods for prostate IMRT.\(^9\)-\(^13\) This study aimed to investigate the efficacy (reproducibility and stability) of our IMRT fixation method using an original knee fixation device (KFD) in terms of residual rotational error and inter-fractional error and examine whether the clinical target volume (CTV) with or without our KFD was within the planning target volume (PTV) margins. Our findings would help evaluate the usefulness of IMRT fixation using the original KFD.

**Methods**

This retrospective study was approved by the Institutional Review Board of the University of Miyazaki Hospital (O-0339). All patients were asked to sign consent forms for participation in the study. Thirty-one male participants were selected among patients who had undergone prostate IMRT between April 2016 and June 2018. The participants were classified into two groups: One group (\(n = 16\); age range: 64–79 years, mean age: 71.9 years) underwent planning CT imaging with the knees fixed in a flexed position using our KFD (knee flexion group [KF]); the other group (\(n = 15\); age range: 64–83 years, mean age: 74.5 years) underwent planning CT imaging without the use of the KFD (knee extension group [KE]). In the KE group, three patients underwent 37 fractions, and 13 patients underwent 39 fractions; in the KE group, one patient underwent 37 fractions, and 14 patients underwent 39 fractions. We compared the distribution of body mass index (BMI) between the two groups using the Cochran-Armitage test for trends to investigate whether there was any dependency on BMI differences between the groups. Subsequent examinations were conducted after confirming no clear difference in the BMI distributions between the groups [Table 1].

CT images were obtained using Optima 580W (GE Healthcare Japan Co., Ltd.). Patients were placed in the supine position. The Dispo NB Board ENB-16 (Engineering System Co., Ltd.) was covered with an ESFORM suction-type fixed bag (Engineering System Co., Ltd.) [Figure 1], and the fixation device was used to stabilize the patient from the back to the tip of the toes. Patients’ abdomens were secured using a thermoplastic shell (Engineering System Co., Ltd.). In the KF group, the KFD (made of Softlon polyethylene foam) was placed at the back of the knees. Softlon, an inexpensive, lightweight, and easy-to-process material, was set on the NB Board. Figure 2 shows a schematic diagram of the proposed KFD. The height of the KFD was set at 10 cm to ensure that the suction-type fixed bag covered the exterior of both knees adequately.

As a pretreatment for both groups, urination was performed for the bladder 1 h before treatment-planning CT and IGRT, and urine was subsequently kept until the end of treatment. In the rectum, if stool or gas was observed during treatment-planning CT or CBCT, the procedure was stopped, and the patient was allowed to defecate. Subsequently, CBCT imaging was performed again to confirm the absence of gas and stool, and IGRT was subsequently performed. During the treatment, three marks were placed on the surface of the patient’s body (front, left, and right) and were used for the isocentric alignment of the laser according to the patient setup. Consequently, the on-board imager system of Clinac® IX (Varian Medical System, Inc.) was used to perform CBCT imaging before the therapy. CBCT images were used to align the positions of the prostate (the target) and the positions of the rectum and bladder (organs at risk) during the treatment. Their positions

| Table 1: Demographic information on the patient with both knee fixation group and knee extension group |
| --- |
| **KF** | **KE** |
| **Patients** | 16 | 15 |
| **Age (years) (mean±SD)** | 71.9±5.0 | 74.5±5.1 |
| 60-80 | 16 | 14 |
| >80 | 0 | 1 |
| **BMI (mean±SD)** | 22.9±2.6 | 22.4±2.6 |
| <20 | 2 | 1 |
| 20-35 | 8 | 11 |
| Missing data | 6 | 3 |

KF: Knee fixation, KE: Knee extension, SD: Standard deviation, BMI: Body mass index
were matched using the auto-matching function of the ARIA Offline Review. The three-dimensional matching algorithm used “logical AND operators.” An intensity range was set; in contrast, structure volume of interest (VOI) was not set. The rectangular VOI of the CBCT image registration was set to the small pelvic cavity, and the intensity range was set to -130-350 Hounsfield Unit (HU) to match the bony structures (axial: Pubic symphysis, coronal: Femoral head, and sagittal: Sacrum). After auto-matching, it was confirmed that the registration of the prostate was on the triaxial image of the central part of the prostate, and no significant deviation was observed. In cases wherein automatching was not possible, the anterior-posterior (A-P), superior-inferior (S-I), and R-L directions were manually moved to adjust the yaw, pitch, and roll to match the positions.

If there was a slight change in the rectum size between the planning CT and CBCT, the prostate movement would be minimal. The rectal A-P diameter at the mid prostate level was measured in both groups, and the rectal diameter was compared between the two groups. We also determined the direction of rectal movement in both groups.

Examinations of residual rotational errors and inter-fractional setup error in the two groups

For each coordinate axis (yaw, pitch, and roll), the differences between the isocenter position on the body surface and the isocenter position during the treatment were calculated in the three directions. The residual rotational errors due to the displacements in the three directions were determined for both groups. The values for the coordinate axis differences in the posterior, superior, and right directions were indicated with a plus sign (+). Similarly, a plus sign (+) was used to indicate the pitch in a direction that raised the foot and the roll upward and to the right. The differences between the groups in terms of the displacements along the A-P, S-I, and R-L directions were identified as the “inter-fractional error.” To evaluate the setup fixation accuracy between the groups, the variance in inter-fractional error and residual rotational error in all directions during treatment was compared between the groups using a homoscedasticity test and box plots. Based on the homoscedasticity test results, the mean values were compared between the groups using Welch’s t-test, assuming unpaired unequal variance.

Estimation of planning target volume margins and clinical target volume coverage for logistic regression analysis

The hypothetical PTV margins were set for the CTV of all the cases examined in this study (KF group: 588 cases, KE group: 568 cases). The hypothetical PTV margins were set in 1-mm increments from 0 to 10 mm for the CTV margins. The movements in the three directions for all cases (calculation detailed above) were transformed into a binary variable. “Yes” for CTV coverage indicates that the difference between the hypothetical PTV margins for every 1 mm and the absolute amount of movement was >0 mm, and the CTV was within the PTV margins. “No” for CTV coverage indicates that the difference between the hypothetical PTV margins for every 1 mm and the absolute amount of movement was <0 mm, and the CTV was outside the PTV margins. The ratio of “yes” for CTV coverage in all cases was plotted as the CTV coverage rate for each group. These coverage rates were calculated as follows:

\[
\text{CTV coverage rate} = \frac{\exp(b_0 + b_1 \times \text{margins})}{1 + \exp(b_0 + b_1 \times \text{margins})} \quad \text{Equation 1},
\]

where \(b_0\) and \(b_1\) are regression coefficients.

From the CTV coverage rate curves obtained above, the hypothetical PTV margin that guaranteed 95% CTV coverage was defined as the optimal inter-fractional margin, which is calculated using the following equation at our institution:

\[
\text{Inter-fractional margins (mm)} = \frac{\log_{10}(19-b_0)}{b_1} \quad \text{Equation 2}
\]

Finally, the Fisher’s exact test, using a 2 × 2 contingency table of CTV coverage in the KE group (two-tailed test, 5% level of significance), was used to calculate the odds ratios for CTV coverage in the KF group. CTV coverage with the original KFD was evaluated using the ORs. All statistical analyses
in this study were performed using R version 3.6.1 (R Core Team [2019]).

RESULTS

Direction of rectal movement comparison
The mean differences in rectal diameter between the two groups and between planning CT and CBCT are shown in Table 2. The difference in rectal diameter was significantly smaller in the KF group than in the KE group, but the distance of rectal movement was slight in both groups (KE: -0.09 ± 0.44 mm, KF: -0.06 ± 0.35 mm), and the movement was confirmed to be in the anterior direction.

Analysis of residual rotational errors and inter-fractional setup error
Figure 3 shows the residual rotational errors in the yaw, pitch, and roll between the setup CBCTs and planning CTs. The mean residual rotational setup errors in the yaw and roll were -0.04° and 0.16° for the KF group and -0.21° and 0.21° for the KE group, respectively. A significant difference in the mean residual rotational error in the yaw and roll was observed between the KF and KE groups (yaw: 0.57 [P < 0.001, 95% confidence interval [CI]: 0.12–0.21], roll: 0.62 [P < 0.02, 95% CI: 0.10–0.01]). There was a slight improvement (~0.1°). The mean residual rotational setup errors in the pitch were 0.18° and -0.02° for the KF and KE groups, respectively. The mean residual rotational error was smaller in the KE group; however, there was more variation in expansion from the negative (-) to the positive (+) direction; the KF group exhibited less variation and better positional reproducibility (pitch: 0.45 [P < 0.001, 95% CI: 0.13–0.27]).

Figure 4 shows the inter-fractional error in the A-P, S-I, and R-L directions of the setup CBCTs and planning CTs. The mean inter-fractional errors in the A-P and S-I directions were -2.65 mm and 0.66 mm for the KF group and -3.18 mm and 0.52 mm for the KE group, respectively. In the A-P direction, the inter-fractional error was significantly smaller in the KF group than in the KE group (A-P: 0.64 [P = 0.0051, 95% CI: 0.02–0.09]; however, the improvement was only 0.53 mm. In contrast, there was no significant difference in the inter-fractional error in the S-I or R-L direction between the groups (S-I: 0.72 [P = 0.46, 95% CI: 0.02–0.05], R-L: 1.02 [P = 0.59, 95% CI: 0.02–0.30]).

Estimation of the planning target volume margins and clinical target volume coverage for logistic regression analysis
Figure 5 shows the sigmoid curves between the hypothetical PTV margins and CTV coverage in the two groups. The KF group had higher CTV coverage rates in the A-P and S-I directions. Table 3 shows the inter-fractional margins calculated from the CTV coverage curves when covering 95% of the total CTV coverage rate using equation 2. Table 3 and Figure 5 show that the inter-fractional margins decreased by -1.75 mm in the A-P direction (a reduction of 20.8%) and by -0.7 mm in the S-I direction (a reduction of 12.6%). In contrast, a small increase in the margins was observed in the R-L direction. The ORs for CTV coverage between the two groups are shown in Figure 6. In the A-P and S-I directions, the ORs in the KF group and the KE group were 2.76 (P < 0.001, 95% CI: 1.74–4.49) and 1.74 (P = 0.024, 95% CI: 1.06–2.92),
respectively, confirming that the original KFD had a significant effective CTV coverage.

**Discussion**

In this study, the mean residual rotational error improved significantly in the KF group compared with the KE group in yaw and roll directions [Figure 3]. Figure 7 shows the residual rotational errors in the pitch direction for each fraction. Our findings revealed the difficulty in adjusting the pitch using surface marks. The residual rotational errors in the pitch of the pelvis between the treatment planning stage and the actual treatment showed fewer disparities in the KF group.
group than in the KE group. Notably, almost no residual rotational error in the negative (-) direction, i.e., along the “foot downward” direction, was observed. As the number of treatments increased in the KE group, the residual rotational error in the pitch direction supposedly led to the reproducibility of the body position. This improvement would be very useful for 4-DoF couch-equipped devices that cannot compensate for the pitch direction. For inter-fractional error, while a reduction of 0.5 mm was obtained in the KF group compared to the KE group in the A-P direction, the value was negligible.

The study showed that the use of the original KFD improved the residual rotational error and inter-fractional error in the A-P direction; however, the difference was extremely small and was not within the setup margins, indicating that the benefit of the KFD was not so clinically significant. However, the increased stability in the body position (especially in the pitch direction) by the original KFD could reduce the burden on the surgeon during the actual setup. In addition, the accuracy of the IMRT fixation device used was almost equal to that of each IMRT fixation device examined by Inui et al. [14]. Indeed, the devices used in this study (including the original KFD) have the same capabilities as other fixation devices.

We calculated PTV margins and CTV coverage using logistic regression analysis to examine the usefulness of the original KFD. The PTV margins (mm) in the KF group shrank by 20.8% in the A-P direction and 12.6% in the S-I direction, thereby confirming the effects of the original KFD. Additionally, these were very close to the margins calculated using the Van Herk formula (2.5 Σ + 0.7 σ) [Table 3]. [15] Our findings demonstrate the validity of our method for estimating the statistically optimal inter-fractional margins using a CTV coverage regression model estimation. The margin calculation method may equally be applicable to other IGRT devices. The existence of the CTV within the hypothetical PTV margin was determined based on a binarization transformation.

Further, the ORs for CTV coverage in the KF group were 2.76 ($P < 0.001$) in the A-P direction and 1.74 ($P = 0.024$) in the S-I direction, indicating that IMRT fixation with the original KFD not only reduced the inter-fractional setup margins but also improved CTV coverage. Further, the smaller margins and higher ORs in the A-P direction might be due to the elimination of the pitch shift in the negative (-) direction.

Table 3: The inter-fractional margins from the clinical target volume coverage curves when covering 95% of the total clinical target volume coverage rate using logistic regression curve

| Inter-fractional margins (mm) | KF | KE |
|------------------------------|----|----|
| A-P                          | 6.68 (6.18) | 8.43 (8.27) |
| S-I                          | 4.87 (5.83) | 5.57 (6.93) |
| L-R                          | 3.78 (4.07) | 3.50 (3.82) |
| Total                        | 9.09 (9.42) | 10.67 (11.45) |

In parentheses are the inter-fractional margins using the formulae proposed by Van Herk et al. KF: Knee fixation, KE: Knee extension, A-P: Anterior-posterior, S-I: Superior-inferior, L-R: Left-right.
owing to the use of the below-KFD [Figure 7] and smaller margins in the directions of the bladder and rectum, which are at-risk organs above and below the prostate, respectively. This could lead to fewer adverse events involving the bladder and rectum, thus making IMRT fixation with the original KFD a useful method.

This study has several limitations. First, IGRT was used to calculate the setup errors due to pelvic bone matching. In the soft tissue, we were able to confirm that there was little rectal movement, but we were not able to confirm a direct match for the prostate. Therefore, it is necessary to confirm the correlation between the position of the pelvic bone and the prostate marker by placing a gold marker in the prostate. Moreover, the intrafractional error similarly should be analyzed in future studies. Studies that analyzed continuous intra-fractional errors for the prostate have reported that a movement of at least 3 mm occurs during a single treatment. Thus, the setup accuracy should be comprehensively examined by combining target intra-fractional errors with inter-fractional errors. Second, the margin was calculated by statistical optimal inter-fractional margin using a CTV coverage regression model estimation. However, the calculation of margins was limited in prostate IMRT. Hence, further studies are needed to calculate the margins in other sites with the Van Herk formula.

Conclusions
Performing fixation with the knee in a flexed position using an original KFD for prostate IMRT reduced pelvic residual rotational error and inter-fractional error in the A-P direction and improved PTV margins and CTV coverage. Our IMRT fixation method may be useful for improving fixation accuracy during the setup, especially in facilities that use 4-DoF couches.

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Conflicts of interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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