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# Assessment of Daily Replanning and Geometrical Variation of High-dose-rate Brachytherapy for the Prostate

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**Abstract.** *Background: The present study aimed to estimate geometric changes in applicators and prostate over 3 days in patients with high-dose-rate brachytherapy (HDR-BT) and to assess the need for daily replanning. Patients and Methods: This study retrospectively investigated 18 patients who underwent HDR-BT as monotherapy from February 2016 to October 2018. Results: Without replanning, the planning target volume coverage significantly worsened on day 2 ($p<0.001$) and day 3 ($p=0.003$). The minimum dose distributed to the highest irradiated rectal volume of 5 cc became significantly higher on day 2 ($p=0.02$), and the maximum dose distributed to the urethra became significantly higher on day 2 ($p=0.01$). Conclusion: Conformal, high-dose delivery of HDR-BT is impaired without replanning not only on the second day but also on the third day. Daily replanning is required for achieving accuracy of HDR-BT.*

High-dose-rate brachytherapy (HDR-BT) provides conformal, high-dose delivery and reduces exposure of surrounding normal tissue by adjusting the dwell position and time. Some research groups have suggested that prostate HDR-BT as monotherapy is only suitable for low- and intermediate-risk patients (1-4). However, HDR-BT is thought to be sufficient treatment for intermediate- and high-risk prostate cancer, which actually or potentially has a risk of extracapsular invasion. This is because applicators can be placed outside of the prostate, and delivery to the outside of the prostate capsule can be performed. Our research group reported a good outcome of HDR-BT as monotherapy for intermediate- and high-risk prostate cancer (5).

The dosimetric advantage of HDR-BT relies on the correct positioning of applicators to the prostate and the organs at risk. Several studies have reported that displacement of applicators occurs between fractions, and conformal, high-dose delivery is not achieved if adequate correction cannot be performed (6-8). However, there are no standard criteria for correcting the treatment plan, such as through the correction of an applicator or replanning, and the optimum correction method is unclear.

Hoskin *et al*. reported that possible causes of movement of applicators were displacement of the external applicator, movement of the prostate, and tissue oedema between the apex of the prostate and perineum (6). To the best of our knowledge, no reports have described quantitative assessment of perineal oedema. In evaluation of changes in a dose–volume histogram, several reports have shown that changes occur from the first to the second day but few reports have shown changes after the second day (6-9). Therefore, some correction, such as correction of applicators or replanning appears to be necessary on the second day but whether correction on the third day is necessary is unclear.

The present study aimed to estimate geometric changes in applicators and the prostate over 3 days in patients with HDR-BT and to assess the need for replanning. We conducted 3-day brachytherapy with treatment plans every day.

## Patients and Methods

*Patient characteristics*. This study was conducted on intermediate- and high-risk patients with prostate cancer who underwent HDR-BT as monotherapy from February 2016 to October 2018. Risk assessment was based on the National Comprehensive Cancer Network guideline (4). All patients participated in a phase II clinical trial of high-dose-rate interstitial radiation monotherapy for

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intermediate and high-risk prostate cancer. The trial was approved by Osaka University Clinical Research Review Committee (UMIN000020206). Written informed consent was obtained from all patients.

*Treatment*. The patients were treated by prostate HDR-BT as monotherapy with a total dose of 40 Gy per five fractions over 3 days. Treatments were performed on day 1 (first treatment), day 2 (second and third treatments), and day 3 (fourth and fifth treatments), with an interval between treatments of at least 6 hours. On days 1, 2, and 3, approximately 1, 21, and 46 hours after insertion of the applicators, a computed tomographic (CT) scan was performed. On day 1, transrectal ultrasonography was used for image-guided insertion of 6-French plastic needles (ProGuide; Elekta Ltd., Stockholm, Sweden) in the lithotomy position under epidural anaesthesia. Before insertion of the applicators, two fiducial gold markers were implanted in the apex and base of the prostate as markers for recognizing the relative position of the prostate and the needles. The procedures for implantation were described in more detail elsewhere (10). After implantation, the lithotomy position was released, and a CT scan was performed in the supine position. From 30 minutes to 1 hour before planning CT scanning, the urethral catheter was clamped, and images were acquired under urine collection. Treatment planning was performed with Oncentra (version: 4.5.1; Elekta Ltd.). The clinical target volume (CTV) was set around the prostate and the proximal lesion of the seminal vesicles, and the planning target volume (PTV) was set equal to the CTV. Dose delivery was manually adjusted with the 2.5-mm step dwelling position to obey the dose constraints. The dose constraints that were used are shown in Table I.

For most cases, the second CT scan was performed before the second treatment and the third scan was performed after the fourth treatment. Daily replanning included re-delineation of target volumes. The second plan was used in the second, third, and fourth treatments, and the third plan was used for the fifth treatment.

*Assessment of coordinates of each point*. CT images on days 2 and 3 were matched with and registered to the CT image from day 1. An automatic registration (bone-based) function of a Raystation (version: 6.2.0; RaySearch Laboratories AB, Stockholm, Sweden) was used. The slice interval of CT was 1.25 mm for 16 cases and 2 mm for two. The change in slice interval was due to replacement of the CT device. To identify the tip of the applicator, an air column was used, which appeared as a black spot on CT. The centre of the air column was recorded as the tip of needle in the CT slice immediately before the disappearance of the applicator. The applicator insertion point at the skin surface was defined as the coordinates where the applicator was covered by 50% or more of the perineal skin. The vectors from the tips of the needles of days 1-3 to the insertion point were determined for the insertion direction of each applicator. The distance of the craniocaudal coordinate between the applicator insertion point of a particular day and the previous day was defined as perineal oedema in each case (Figure 1A). The central coordinates of each fiducial marker were defined as the coordinates of the fiducial marker. The change in distance between two fiducial markers was used as an index of prostate oedema, as described in previous studies (Figure 1B) (11, 12). We measured the midpoint of the fiducial markers for days 1, 2 and 3, and measured the displacement lengths of the perpendicular and parallel directions to the applicator from day 1 to 2 and from day 2 to 3. This change was considered as the distance in movement of the prostate (Figure 1C). The concept of the analyses is shown in Figure 1. Each analysis was measured by the same observer and reviewed by another Radiation Oncologist.

Table I. *The study dose constraints*.

| Target volume/organ at risk | Dosimetric objective |
|---|---|
| PTV | D95 ≥8 Gy |
| Rectum | D5cc <4.4 Gy |
| | Dmax <8 Gy |
| Urethra | Dmax <10 Gy |

PTV: Planning target volume; D95: minimum coverage dose of 95% of the PTV, D5cc: minimum dose distributed to the highest irradiated volume of 5 cc of the rectum; Dmax: maximum dose distributed to the rectum or the urethra.

*Assessment of the dose–volume histogram*. Two virtual plans were made for each case as follows: One plan on day 2 CT with the day 1 source position and dwelling time; and one plan on day 3 CT with the day 2 source position and dwelling time. The dose distribution was calculated using Oncentra with consideration of the shifted dwell positions. The minimum coverage dose of 95% of the PTV (PTV D95%), the minimum dose distributed to the highest irradiated rectal volume of 5 cc (rectal D5cc), and the maximum dose distributed to the urethra (urethral Dmax) were calculated.

*Analysis*. Statistical analyses were performed using JMP Pro (version 13; SAS Inc., Cary, NC, USA). Two-sided tests were performed for geometric variations from day 1 to 2, from day 2 to 3, and for the dose–volume histogram with and without replanning on day 2 and 3. Differences with a value of $p<0.05$ were considered statistically significant.

## Results

A total of 18 patients were included in the study and their background data are shown in Table II.

For days 1 to 2 and days 2 to 3, the mean [±standard deviation (SD)] change in perineal oedema was −5.5±0.24 mm ($p<0.001$) and −0.6±2.4 mm ($p=0.33$), respectively. The corresponding mean prostate movement for day 1 to 2 and day 2 to 3 was 3.1±0.24 mm ($p<0.001$) and 0.0±0.19 mm ($p=0.93$), respectively. Negative values indicate displacement in the caudal direction, whereas positive values indicate displacement in the cranial direction. The distance between fiducial markers increased by 5.4%±2.9% from day 1 to 2 ($p<0.001$) and by 1.4%±2.8% from day 2 to 3 ($p=0.04$).

Figure 2 shows the changes in PTV D95%, rectal D5cc, and urethral Dmax for days 1, 2, and 3 between the actual plan and the hypothetical plan. Without replanning, PTV coverage significantly worsened on day 2 ($p<0.001$) and day 3 ($p=0.003$). Rectal D5cc became significantly higher on day 2 ($p=0.02$), while urethral Dmax became significantly higher

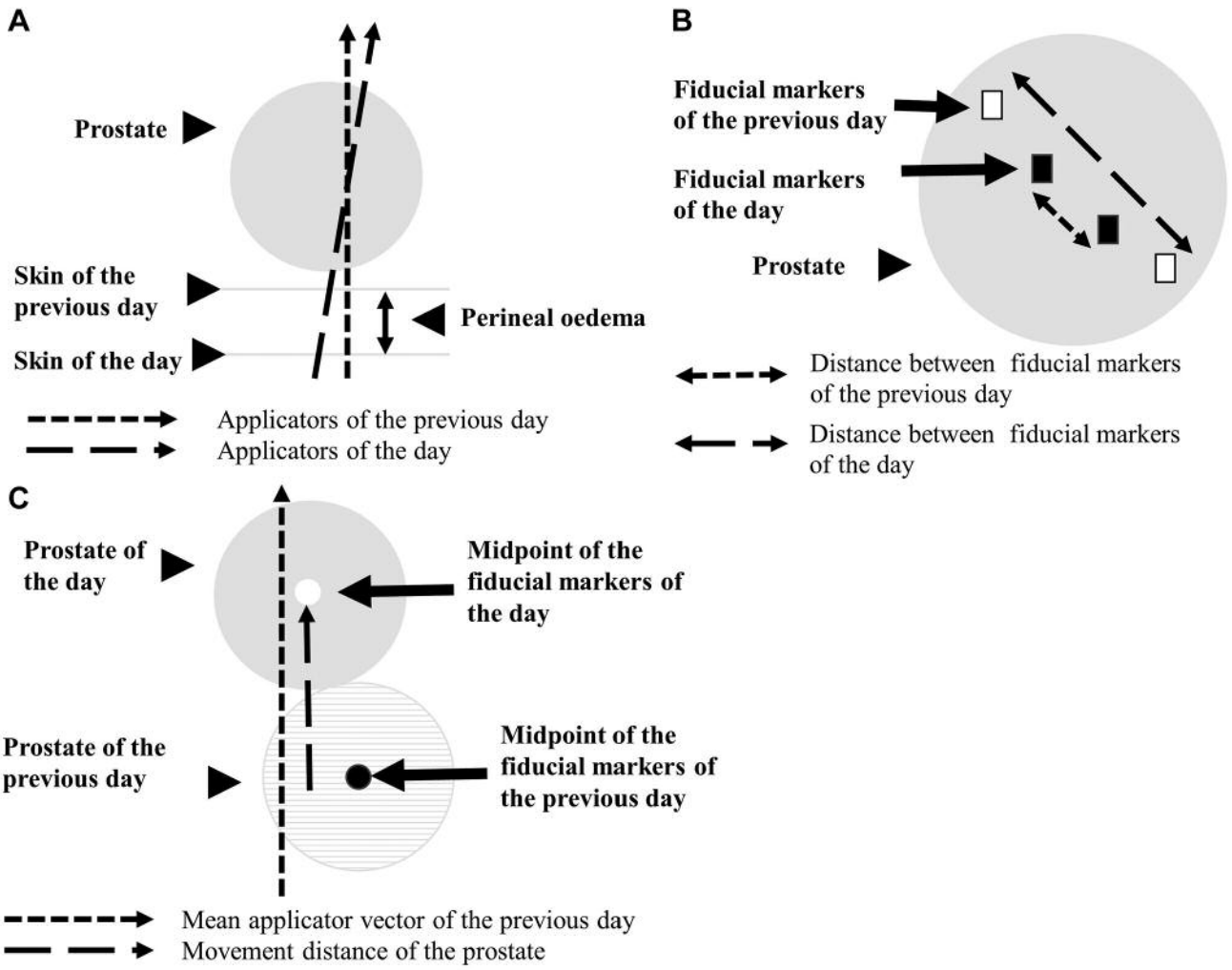


Figure 1. *Methods for measuring perineal oedema (A), prostate oedema (B) and prostate movement (C).*

on day 2 ($p$=0.01) and had a tendency to become higher on day 3 ($p$=0.09). PTV significantly increased from day 1 to 2 ($p$=0.009), while no obvious increase was observed from day 2 to 3 ($p$=0.22).

## Discussion

HDR-BT for prostate cancer has a good dose concentration based on the accuracy of delivery and it relies on geometrical reproducibility of applicators. However, displacement of applicators may occur between fractions and the reliability of treatment is reduced if displacement occurs. In fractionated HDR-BT, ensuring geometrical reproducibility is important for dose concentration (6-9, 13). To solve this issue, in our study, we replanned every day using daily CT simulation images. Previous reports on the reproducibility of prostate HDR-BT suggested that a change in displacement occurs on the second day (9, 12). Takenaka *et al*. reported that the largest change in applicator displacement occurs from the first to the second day, and the change from the second to the fourth day is small (9). Similarly, in this study, the main geometric changes occurred from day 1 to 2, while mild prostate oedema occurred from day 2 to 3.

In our study, perineal oedema, movement of the prostate, and prostate oedema mainly occurred from day 1 to 2 and only prostate oedema occurred between day 2 and 3. Previous studies have shown that a larger amount of oedema occurs on the second than the third day (7, 8), which the finding from our study is consistent with. Perineal oedema and movement of the prostate cause displacement of applicators, resulting in changes in dose distribution. Controlling perineal oedema and movement of the prostate

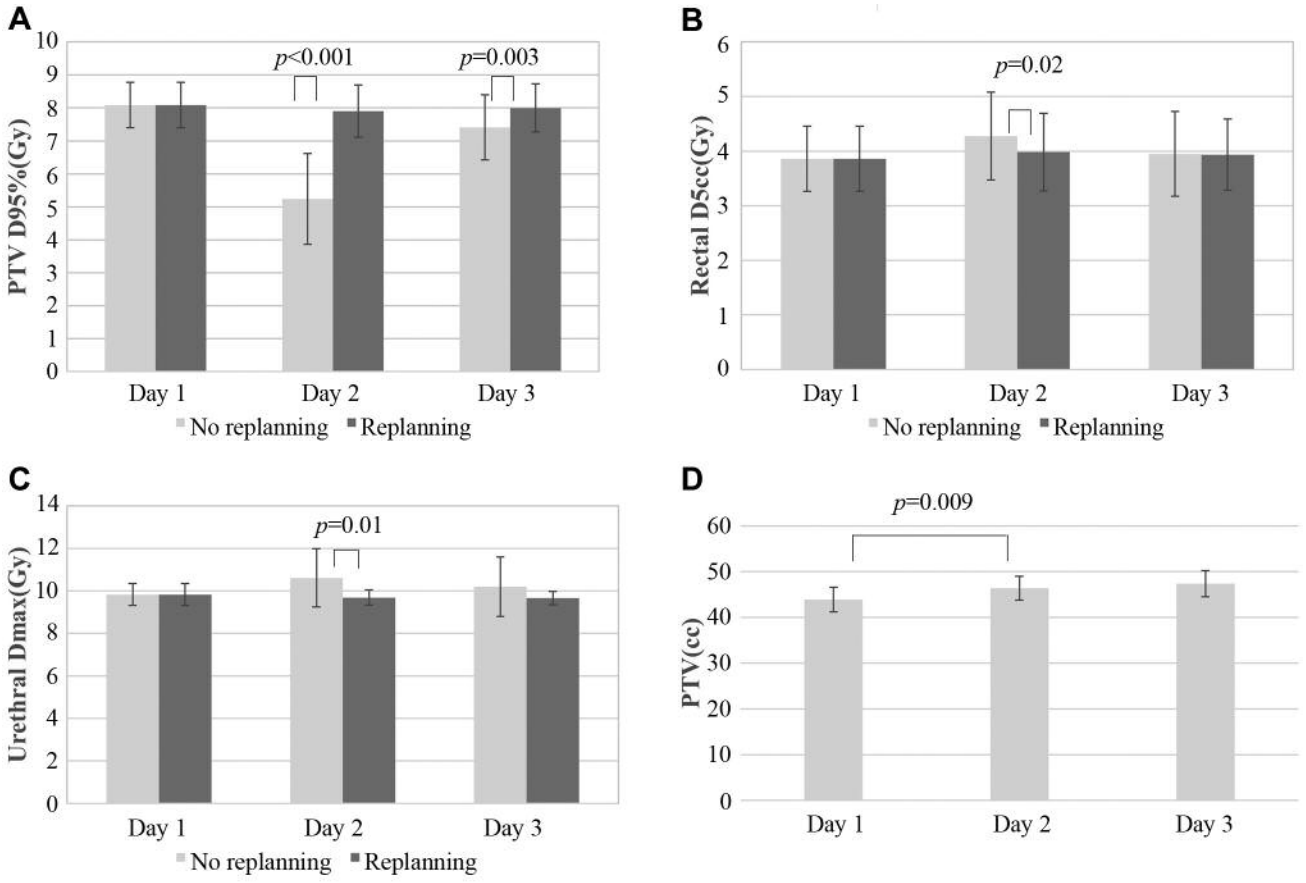


Figure 2. *Changes in the minimum coverage dose of 95% of the PTV, D5cc: Minimum dose distributed to the highest irradiated volume of 5 cc of the rectum; Dmax: maximum dose distributed to the urethra for days 1, 2, and 3 between the actual plan and the hypothetical plan. Without replanning, on days 2 and 3, computed tomography used the previous day's source position and dwell time. Data are means±standard error of the mean.*

medically is difficult, and therefore, changes in dose distribution are also difficult to control. Consequently, we consider that daily correction is necessary in a multifractionated HDR-BT for prostate cancer. Several studies reported that prostate oedema was generated by insertion of an applicator (1, 11, 12, 14). In our study, the distance between fiducial markers increased by 5.4% from day 1 to 2, which suggested that prostate oedema occurred to a similar extent as the distance between fiducial markers. Owing to the fact that geometric deformation occurs because of prostate oedema, CT scans should be performed for planning and replanning, as well as for correction of applicator displacement. In the current study, PTV increased from day 1 to 2 by replanning. This finding suggests that the irradiated area would be insufficient without replanning and daily re-delineation of target volumes is necessary.

Without replanning, a significant decline was observed in PTV D95% on days 2 and 3. Rectal D5cc and urethral Dmax became significantly higher on day 2 than day 1. No significant increase in rectal D5cc was observed on day 3. Without replanning, urethral Dmax on day 3 tended to increase compared to when replanning. Previous studies have reported that coverage of the PTV may worsen without a correction in treatment plan on the second day (6, 8, 13), which is supported by our study. Takenaka *et al*. suggested that a cranial margin of 15 mm appeared to be effective to maintain the CTV D90% level without corrective action, even on the third day (9). We set the PTV equal to the CTV in our study. This strategy reduced the PTV, and the doses of the urethral bulb and bladder neck, which are associated with urinary toxicity and sexual dysfunction (15, 16), were also thereby reduced. We showed that daily replanning was necessary to maintain coverage of the PTV when the PTV was set equal to the CTV.

One of the limitations of this study was intra- and interobserver variability of contouring the prostate, seminal vesicles, and organs at risk. Fiorino *et al*. reported that the short-term intraobserver variability in contouring the volume of the prostate and seminal vesicles was 5%, and interobserver variability ranged from 10% to 18% (17). Although intraobserver variability may reduce PTV D95%,

Table II. *Patient characteristics (n=18).*

| Characteristic | Value |
|---|---|
| Age, years | |
| Median (range) | 70.5 (54-76) |
| Number of applicators | |
| Median (range) | 16.5 (14-18) |
| Gleason score, n (%) | |
| 6 | 0 (0) |
| 7 | 11 (61) |
| ≥8 | 7 (39) |
| Clinical T stage, n (%) | |
| T1c-T2a | 3 (17) |
| T2b-T2c | 8 (44) |
| ≥T3a | 7 (39) |
| Initial PSA, ng/ml | |
| Median (range) | 11.7 (4.4-68.9) |
| Pretreatment ADT, n (%) | |
| Yes | 15 (83) |
| No | 3 (17) |
| NCCN risk group, n (%) | |
| Intermediate | 4 (22) |
| High | 14 (78) |

PSA: Prostate-specific antigen; ADT: androgen deprivation therapy; NCCN, National Comprehensive Cancer Network.

in this study, we did not distinguish whether PTV D95% was caused by a geometrical change or by intraobserver variability.

## Conclusion

This study shows that conformal, high-dose delivery of HDR-BT is impaired without replanning. Target re-delineation and treatment replanning are necessary on the second day. Even on the third day, replanning is important for achieving accuracy of treatment because prostate oedema, which potentially causes a change in the dose distribution, can occur even on the third day.

## Conflicts of Interest

None.

## Authors' Contributions

Conceptualization: Hirofumi Uchida, Keisuke Otani and Yasuo Yoshioka. Funding acquisition: Kazuhiko Ogawa. Data curation: Hirofumi Uchida, Takero Hirata, Michio Oda, Yuichi Akino and Iori Sumida. Formal analysis: Hirofumi Uchida. Investigation: Hirofumi Uchida, Takero Hirata, Keisuke Otani, Daisuke Eino. Supervision: Keisuke Otani, Osamu Suzuki, Michio Oda, Yuichi Akino, Iori Sumida, Koji Hatano, Kazutoshi Fujita, Motohide Uemura, Ryoichi Imamura, Yasuo Yoshioka, Norio Nonomura and Kazuhiko Ogawa. Writing: Hirofumi Uchida and Takero Hirata.

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