High-dose-rate interstitial brachytherapy for gynecologic malignancies—dosimetric changes during treatment period

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To overcome cranio-caudal needle displacement in pelvic high-dose-rate interstitial brachytherapy (HDRIB), we have been utilizing a fullystretched elastic tape to thrust the template into the perineum. The purpose of the current study was to evaluate dosimetric changes during the treatment period using this thrusting method, and to explore reproducible planning methods based on the results of the dosimetric changes. Twenty-nine patients with gynecologic malignancies were treated with HDRIB at the Cancer Institute Hospital. Pre-treatment and post-treatment computed tomography (CT) scans were acquired and a virtual plan for post-treatment CT was produced by applying the dwell positions/times of the original plan. For the post-treatment plan, D90 for the clinical target volume (CTV) and D2cc for the rectum and bladder were assessed and compared with that for the original plan. Cranio-caudal needle displacement relative to CTV during treatment period was only 0.7 ± 1.9 mm. The mean D90 values for the CTV in the pre- and post-treatment plans were stable (6.8 Gy vs. 6.8 Gy) and the post-treatment/pre-treatment D90 ratio was 1.00 ± 0.08. The post-/pre-treatment D2cc ratio was 1.14 ± 0.22 and the mean D2cc for the rectum increased for the post-treatment plan (5.4 Gy vs. 6.1 Gy), especially when parametrial infiltration was present. The mean D2cc for the bladder was stable (6.3 Gy vs. 6.6 Gy) and the ratio was 1.06 ± 0.20. Our thrusting method achieved a stable D90 for the CTV, in contrast to previous prostate HDRIB reports displaying reductions of 35–40% for D90 during the treatment period.

Keywords: interstitial brachytherapy; needle displacement; gynecologic malignancy; dose–volume histogram

INTRODUCTION

For gynecologic tumors unsuitable for standard intracavitary brachytherapy, such as recurrent tumors or tumors with excessive invasion to the vagina/parametrium, interstitial brachytherapy has been used to achieve better tumor coverage [1–3]. Contemporary planning software for high-dose-rate interstitial brachytherapy (HDRIB) using pre-treatment computed tomography (CT) images enables a conformal dose distribution to a target, while minimizing doses to organs at risk (OARs). To reproduce the plan in actual irradiation, relative locations of applicator needles to the clinical target volume (CTV) and OARs should also be reproduced exactly at each treatment session. However, in the literature on prostate HDRIB, needle displacements as high as 18–42 mm in the cranio-caudal direction have been reported, resulting in decreases of 35–40% in CTV coverage [4–7]. Displacements in other directions have never been explored. The needle-template unit in these studies was not sufficiently stabilized to a target. To overcome the caudal force exerted by perineal edema, we have been utilizing cranial force from fully stretched elastic tapes thrusting the template into the perineum. The purpose of the current study was to explore dosimetric changes caused by these dimensional (3D) displacements and organ mobility or...
deformation, to ensure safe delivery of the HDRIB treatment. To the best of our knowledge, this is the first study to report dose–volume histogram (DVH) changes during the treatment period for gynecologic HDRIB.

**MATERIAL AND METHODS**

**Patients**

Between March 2006 and October 2008, 29 patients with gynecologic cancer (cervix 21, corpus 7, vulva 1) were treated at the Cancer Institute Hospital using HDRIB in combination with/without external beam radiotherapy. Patient characteristics are summarized in Table 1. Fourteen patients displayed non-recurrent disease, and 15 patients displayed recurrent disease following surgery (n = 12), radiation (n = 1) or both (n = 2).

**Methods**

**Implantation and CT acquisition**

Thirteen patients were treated with tandem and needles and 16 patients with needle alone. Mean number of needles used was 18 ± 4 (range 9–28). All needles and the template were unified with stopper screws and the template was sutured to the perineum using six silk stitches. To overcome the caudal movement resulting from perineal edema, the needle-template unit was thrust into the perineum using two fully stretched elastic tapes of about 30 cm in length (ELASTIKON®; Johnson & Johnson, New Brunswick, NJ) attached from the ventral skin near the umbilicus through both sides of the template to the dorsal skin at the umbilical level.

About 3 h after implantation, pre-treatment CT for planning was performed. A post-treatment CT was taken prior to removal of the implant after the last treatment session. Both CT scans were performed with the bladder filled with about 200 ml saline. The interval between the two CTs was 3.4 ± 0.8 days (range 2–6 days).

**Treatment planning**

Planning was performed using pre-treatment CT data transferred to a planning computer (PLATO BPS® ver. 14.3.5; Nucletron, Veenendaal, the Netherlands). A central plane and the basal dose points were determined according to the extrapolated Paris system. Geometrical optimization with manual adjustments was used to achieve CTV coverage, and to keep doses for OARs below ceiling doses, and to keep hyperdose sleeves within 8–10 mm. When these three conditions (CTV coverage, OAR doses, hyperdose sleeve) could not be achieved simultaneously, the plan was clinically compromised. The selected isodose surface (85.4 ± 2.4% basal dose isodose surface (BDIS)) covering CTV was essentially chosen for dose prescription. The prescribed dose was 6.0 Gy per fraction to this isodose surface.

**Organ delineation**

For each set of CT images, the CTV, rectum, bladder and the urethra were delineated by a single radiation oncologist (T.O.) and reviewed by another who is certified (T.N.) to eliminate inter-observer variation. The CTV, including all the areas of gross and potentially microscopic disease which consisted of the vagina, the parametrial tissues and the uterus, was delineated on each slice using clinical information, CT/magnetic resonance imaging (MRI) and the implanted markers. For OARs, only the outer surface of the rectum, bladder and urethra were contoured and all of the volume inside the outer surface was utilized for the indices following GEC-ESTRO recommendations [8]. The rectum was delineated from the sigmoid colon curvature to the caudal level of ischial tuberosity. For the urethra, the outer surface of the Foley catheter was contoured from the bladder base to the external urethral meatus.

**Dosimetric analysis**

A virtual plan for post-treatment CT was produced by duplicating the air kerma strength for the Ir-192 source, the dwell times and positions of the original plan. Dosimetric analysis was performed using the GEC-ESTRO recommendations [8]. To evaluate the coverage of the target, the dose received by 90% of the CTV (D90) was generated. For
OARs, the minimum doses to the most irradiated 2 cm³ portions (=D2cc) for the rectum and bladder were generated. The dose to 50% of the urethra (=D50) was evaluated according to a study by Akimoto [9]. For each index, % BDIS and the ratio of post-treatment value to pre-treatment value was generated. All statistical analyses were performed using Dr.SPSS II (SPSS, Chicago, IL, USA). The Wilcoxon signed-rank test was used to compare DVH parameters between pre-treatment and post-treatment plans.

RESULTS

Needle displacement relative to CTV centroid
Needle displacement relative to CTV centroid during treatment period was 0.5 ± 2.1 mm in the lateral direction (minus (right)–plus (left)), 1.6 ± 3.9 mm in the dorso-ventral direction (minus (dorsal)–plus (ventral)) and –0.7 ± 1.9 mm in the crano-caudal direction (minus (caudal)–plus (cranial)).

Volumetric and dosimetric results of the CTV and OARs
The volumetric and dosimetric results of CTV and OAR for the rectum, bladder and urethra are presented in Table 2. The CTV volumes showed a slight decrease during treatment (77.7 ± 45.5 cm³ vs. 73.8 ± 41.1 cm³), but the CTV doses were stable for both D90 values (6.8 ± 0.7 Gy vs. 6.8 ± 0.9 Gy). No difference was seen in the volumes for OARs between the pre- and post-treatment plans, but dosimetric results varied among the organs. For the rectum, the mean D2cc increased from 5.4 Gy ± 1.1 Gy to 6.1 Gy ± 1.5 Gy (P< 0.01). For the bladder, the mean D2cc tended to increase from 6.3 ± 1.8 Gy to 6.6 ± 2.1 Gy (P= 0.16). The mean D50 values for the urethra in the pre- and post-treatment plans were 3.7 ± 1.1 Gy vs. 3.6 ± 1.0 Gy (P= 0.22).

Table 2. Volumetric results in CTV and OARs (rectum, bladder, urethra and sigmoid colon)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Pre-treatment plan</th>
<th>Post-treatment plan</th>
<th>Post/pre ratios</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>77.7 ± 45.5 cm³</td>
<td>73.8 ± 41.1 cm³</td>
<td>0.96 ± 0.09</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>(range 7.1–180 cm³)</td>
<td>(range 6.4–172.4 cm³)</td>
<td></td>
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<tr>
<td>Rectum</td>
<td>71.8 ± 30.5 cm³</td>
<td>76.7 ± 32.5 cm³</td>
<td>1.18 ± 0.68</td>
<td>P = 0.52</td>
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<tr>
<td></td>
<td>(range 33.7–193.0 cm³)</td>
<td>(range 25.6–149.6 cm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>255.1 ± 67.9 cm³</td>
<td>250.8 ± 62.5 cm³</td>
<td>1.04 ± 0.37</td>
<td>P = 0.75</td>
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<tr>
<td></td>
<td>(range 80.2–392.8 cm³)</td>
<td>(range 122.7–398.9 cm³)</td>
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<td></td>
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<tr>
<td>Urethra</td>
<td>1.2 ± 0.3 cm³</td>
<td>1.2 ± 0.3 cm³</td>
<td>0.99 ± 0.04</td>
<td>P = 0.70</td>
</tr>
<tr>
<td></td>
<td>(range 0.5–1.9 cm³)</td>
<td>(range 0.4–1.8 cm³)</td>
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</tr>
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</table>

Dosimetric analysis for the CTV and OARs
The post-/pre-treatment D90 ratio for the CTV was 1.00 ± 0.08 (range 0.83–1.26). For 72.4% (=21/29) of the patients, the difference between pre- and post-treatment D90 for the CTV was within ±5%. The post-/pre-treatment D90 ratio was poorly correlated with cranio-caudal needle displacement: 0.95 ± 0.09 with displacement ≥3.0 mm (n= 4) vs. 1.01 ± 0.07 with displacement <3.0 mm (n= 25). Volume changes for the CTV also had little influence on the post-/pre-treatment D90 ratios, which were 1.01 ± 0.08
in cases with volume increase ($n = 9$) vs. 0.97 ± 0.05 in cases with volume reductions ($n = 20$).

The post-/pre-treatment D2cc ratios for the rectum and bladder were 1.14 ± 0.22 (range 0.71–1.63) and 1.06 ± 0.20 (range 0.67–1.48), respectively. The post-/pre-treatment D2cc ratio for the rectum was significantly higher when parametrial infiltration was present (1.22 ± 0.11, $n = 17$) than when absent (1.02 ± 0.15, $n = 12$). The post-/pre-treatment D2cc ratio for the bladder was significantly higher when tandem use was present (1.23 ± 0.24) than when absent (1.06 ± 0.16), and also higher when cranio-caudal displacement was <3.0 mm (1.09 ± 0.20), compared with displacement >3.0 mm (0.90 ± 0.10). Lower vaginal infiltration and post-hysterectomy status showed little impact on dosimetry for the CTV and OARs (Table 3).

Figure 1 shows the frequency distributions of the post-/pre-treatment D90 ratios for the CTV and OARs. The distribution for the D90 ratio shows a narrow range with a large peak at around 1.00, whereas the distribution for D2cc ratios for the rectum and bladder displayed a relatively wide distribution. The urethra D50, however, showed a narrow range with a peak at around 1.00 similar to the distribution for the D90 ratio for the CTV.

**Dosimetric analysis (%BDIS)**

For %BDIS of mean dose at pre-treatment planning, the CTV mean was the highest (140.1 ± 30.3%) followed by that of the urethra (52.5 ± 15.1%), rectum (36.3 ± 9.8%) and bladder (24.1 ± 7.7%). The pre-treatment %BDIS of rectal D2cc was higher when parametrial infiltration was present (85.2 ± 9.1%) than when absent (73.5 ± 18.1%) ($P = 0.05$). To assess the relationships between relative locations of CTV for each OAR and applicator, a scattergram was generated comparing the post-/pre-treatment dose ratios and %BDIS at pre-treatment planning (Fig. 2a and b). For CTV D90 and urethra D50, the ratios were distributed around 1.00 regardless of the pre-treatment %BDIS of the mean dose. The post-/pre-treatment ratios for D2cc for the rectum in cases with %BDIS of D2cc at pre-treatment planning $\leq 90\%$ and $>90\%$ were 1.20 ± 0.19 and 0.91 ± 0.19 ($P = 0.03$). The corresponding ratios for bladder D2cc were 1.10 ± 0.21 and 1.03 ± 0.18 ($P = 0.31$).

**DISCUSSION**

Recent planning software for HDRIB enables conformal dose distribution to a target, while minimizing doses to OARs. According to the ICRU 58, PTV is identical to CTV since the applicators move with the CTV [10] and relative locations of brachytherapy needles should be identified at each treatment session to reproduce the plan in actual irradiation. In previous reports for prostate HDRIB, however, only cranio-caudal needle displacements have been explored and have been reported to peak as high as 18–42 mm, which caused a reduction in the D90 for the prostate of 30–40% [4–7]. In our study, cranio-caudal displacement was only 0.7 ± 1.9 mm, obtained by using our fixation method with fully stretched elastic tapes.
Fig. 1. Frequency distribution chart for post-/pre-treatment ratios of CTV and OARs. (a) Abscissa: post-/pre-treatment ratios of D90 for CTV. Ordinate: number of patients. Distribution approximates Gaussian and has steep peak, with a mean ratio of $1.00 \pm 0.08$. (b) Abscissa: post-/pre-treatment ratios of D2cc for rectum. Ordinate: number of patients. Distribution is negatively skewed and positively shifted, with a mean ratio of $1.14 \pm 0.22$. (c) Abscissa: post-/pre-treatment ratios of D2cc for bladder. Ordinate: number of patients. Distribution is negatively skewed, with a mean ratio of $1.06 \pm 0.20$. (d) Abscissa: post-/pre-treatment ratios of D50 for urethra. Ordinate: number of patients. Distribution is negatively skewed, with a mean ratio of $1.00 \pm 0.12$.

Fig. 2. (a) Correlation between the dose ratio (ordinate: post-/pre-treatment dose ratio) and the relative locations at pre-treatment planning (abscissa: %BDIS (6 Gy = 100%) of mean dose at pre-treatment planning) for CTV and OARs. Red = CTV mean, brown = rectum mean, blue = bladder mean, green = urethra mean. (b) Correlation between the dose ratio (ordinate: post-/pre-treatment dose ratio) and the relative locations at pre-treatment planning (abscissa: %BDIS of D2cc at pre-treatment planning) for rectum and bladder. Brown = rectum, blue = bladder.
Displacements were also shown in other directions, 0.5 ± 2.1 mm in the lateral and 1.6 ± 3.9 mm in the dorso-ventral directions. In pelvic HDRIB, this is the first study to investigate DVH changes of CTV and OARs by these 3D displacements and also to demonstrate DVH changes during gynecologic HDRIB treatment.

In contrast to previous prostate HDRIB reports, D90 for the CTV showed no change between pre-treatment (6.8 ± 0.7 Gy) and post-treatment (6.8 ± 0.9 Gy) and the deviation of the post-/pre-treatment D90 ratio was also small (1.00 ± 0.08). Using our simple fixation method, cranio-caudal needle displacement relative to CTV was nearly negligible and good CTV coverage was obtained during HDRIB treatment. Lateral and dorso-ventral displacements were also small enough that D90 did not change for the CTV.

The resultant CTV coverage and small deviation of the post-/pre-treatment D90 ratio for CTV in the current study are similar to results of our previous in vivo dosimetry study on pelvic HDRIB for 66 patients in which the same fixation method was used [11]. The compatibility ratio of the measured/calculated doses for the target (vaginal wall) was excellent (91 ± 8%). Moreover, a 9% negative shift was considered to be attributed to the lack of inhomogeneity correction in the software for the vaginal cylinder, which has a density of 1.24. The small deviation of the compatibility ratio was largely attributable to our fixation method with fully stretched tape and synchronization in movement and deformation between the CTV and the applicator. The CTV was always deformed slightly due to the surrounding organs, but when the applicators were implanted into the target, a ‘CTV-template-needle complex’ was formed. The target always moved or deformed synchronously with the applicator, and applicator movement in the dorso-ventral or lateral directions had little influence on CTV coverage. Consequently, CTV coverage was not changed between pre-treatment and post-treatment CT.

We found that a large deviation was seen in post-/pre-treatment D2cc for both the rectum and bladder, which was also similar to the results of our in vivo dosimetry study. The rectum and bladder were independently deformed and inflated regardless of applicator movement. As a result, the distance from the applicator was varied during treatment. When the distance from the applicator was reduced, the doses increased. In this study, rectal dose increased from 5.4 Gy to 6.1 Gy and the deviation of post-/pre-treatment D2cc ratio was large (1.14 ± 0.22), and bladder dose tended to increase from 6.3 Gy to 6.6 Gy and the deviation was also large (1.06 ± 0.20). Furthermore, great variability was seen in the post-/pre-treatment volume ratios for both the rectum (1.18 ± 0.68) and bladder (1.03 ± 0.33). The patient must stay in bed during implantation because applicators protrude from the perineum, thus defecation or degassing by her own efforts is quite difficult. Similarly, a predetermined amount of injection into the bladder was sometimes difficult because of severe irritation.

There is not enough space between the rectum and the applicators, so the rectum gets covered by higher dose areas (=6.0 Gy iso-dose line) when expanded. The result of this study indicates that the rectal dose was more easily increased in patients with parametrial infiltration and/or in cases of %BDIS of D2cc for rectum >90% at pre-treatment planning. When parametrial infiltration existed, it was necessary to implant needles in the parametrium, the lateral to the rectum.

![Fig. 3. Transverse CT image of dose distribution of HDRIB planning at the time of (a) the pre-treatment planning and (b) the post-treatment planning. D (reference isodose (6 Gy)) = green, CTV = red, rectum = brown, bladder = blue, urethra = purple. CTV–template-needle complex moved ventrally by rectal inflation or peri-rectal edema during treatment. With our fixation method, cranio-caudal needle displacement was negligible. Dosimetric coverage of CTV was almost unchanged except for the peripheral region of the CTV, which sometimes fell off because of steep dose gradient (dashed orange arrows). Rectum was enlarged during the treatment period and the volume covered with 6-Gy reference isodose was increased (orange arrows).](https://academic.oup.com/jrr/article-abstract/54/4/663/908822)
This method made the rectum expansion restricted, which results the rectal dose being easily increased (Fig. 3a and b). The %BDIS =90% region was nearly equivalent to the region of the peripheral area of the CTV. In cases of %BDIS of D2cc at pre-treatment planning <90%, the organ had inflatable space for applicators while little space was available in cases of %BDIS of D2cc >90%. In order to avoid unexpected higher rectal doses, a degassing method should be considered when rectal inflation is observed with fluoroscopy or CT.

On the other hand, the bladder has enough space to distend ventrally or cranially as well as posteriorly. Therefore, the distance from applicator changes little with changes in bladder volume. In this study, 200 ml saline was injected in each treatment session in order to fill the bladder. In gynecologic brachytherapy, the full bladder technique has been recommended to reduce the dose to the small intestine and sigmoid colon. In some reports for gynecologic intracavitary brachytherapy with CT-based 3D planning, bladder-filling control can lead to a significant reduction in the dose to the small bowel without exceeding the bladder dose [12–13].

In contrast, the post-/pre-treatment D50 ratio for the urethra was 1.00 ± 0.12, showing a similar deviation to D90 for CTV. The scattergram pattern in the urethra also displayed similar characteristics to the CTV D90. The urethra was a less deformed or inflated organ, and applicators were implanted in parallel in the dorsal and lateral spaces of the urethra, urethral movement was synchronized with the applicators and urethral coverage was stable during HDRIB treatment.

To successfully achieve the treatment goal of HDRIB treatment for gynecological malignancies, the first consideration is to have the reproduction of the CTV and the needle-template unit position for each treatment. With our simple fixation method, crano-caudal needle displacement is small and a highly reproducible CTV coverage is expected during HDRIB treatment. To control bladder and rectal volume at each treatment session is also important but is difficult. This requirement can be met by use of the recent image-guided methods, which are capable of providing volume images of soft-tissue organs. If large crano-caudal displacements are confirmed, an increased margin around the CTV or a dose increment for the prescription dose is required as a safety margin. However, these increases need to be evaluated with clinical judgement because D2cc for the rectum and bladder will also rise as a result.

Finally, we used HDRIB with metal applicators in this study. However, metal applicators cause artifacts on CT images, making it difficult to draw organ contours. Some groups are performing image-based brachytherapy by using plastic/titanium applicators compatible with MRI [14–15]. We also plan to start MRI-based image-guided HDRIB.

In conclusion, with our simple method of fixing the needle-template unit using elastic tapes, needle displacement relative to the CTV was nearly negligible and excellent CTV coverage was achieved at the final treatment session. The difference between pre- and post-treatment D90 for the CTV was within ±5% for 72.4% (21 of 29) of the patients in most cases.

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