Daily CT Measurement of Needle Applicator Displacement during Multifractionated High-dose-rate Interstitial Brachytherapy for Postoperative Recurrent Uterine Cancer

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Needle applicator displacement/Corrective action/High-dose-rate interstitial brachytherapy/Recurrent uterine cancer.

We investigated daily needle applicator displacement during multifractionated high-dose-rate interstitial brachytherapy (HDR-ISBT) for postoperative recurrent uterine cancer. Eight patients with postoperative recurrent uterine cancer received HDR-ISBT with or without external beam radiotherapy using our unique ambulatory technique. To analyze displacement, we obtained daily computed tomography (CT) images for 122 flexible needle applicators at 21, 45, 69, and 93 hours after implantation. Displacement was defined as the length between the center of gravity of titanium markers and the needle applicator tips along the daily CT axis. For cases in which displacement was not corrected, we also calculated the dose that covered 90% of the clinical target volume (D90(CTV)) using a dose–volume histogram (DVH). Median caudal needle applicator displacement at 21, 45, 69, and 93 hours was 3, 2, 4, and 5 mm, respectively. More than 15 mm displacement was observed for 2% (2 of 122) and 17% (10 of 60) of needle applicators at 21 and 93 hours, respectively. Cases in which dwell positions were not changed to correct the treatment plan, 2 of 8 patients showed more than 10% reduction in D90(CTV) values compared with the initial treatment plan. Correction of dwell positions of the treatment source improves treatment DVH for multifractionated HDR-ISBT.

INTRODUCTION

Early-stage uterine cancer has a high cure rate with radical surgery. However, radical treatment becomes difficult if the tumor recurs locally. Interstitial brachytherapy (ISBT) is a viable option for massive vaginal or parametrial tumor lesions; treatment outcomes have been favorable. Weitmann et al. reviewed the results obtained from 6 institutes; they found local control and overall survival rates of 29%–100% and 56%–63%, respectively.1) To improve results of ISBT, image-guided implantation involving imaging techniques such as ultrasonography (US),2–3) computed tomography (CT),4,5) or magnetic resonance imaging (MRI) has been explored.6) These innovative techniques will help identify postoperative recurrent tumors, which are often large and have complicated shapes, making them difficult targets for adequate free-hand implantation. Therefore, we introduced transrectal ultrasonography (TRUS)-guided implantation and MRI-assisted CT treatment planning for our high-dose-rate (HDR) ISBT (HDR-ISBT) cases. Simultaneously, we used an ambulatory technique7–9) in which flexible applicators enabled patients to walk during the treatment period. Patients became free of metallic items used for treatment and underwent MRI. We initially used this technique in prostate cancer patients7) and then in previously untreated uterine cervical cancer patients.8) We performed free-hand implantation without a template because implantation of a parametrial extension is easier without pubic arch interference. Imaging modality guidance has been shown to be useful for achieving adequate free-hand implantation. Recently, we reported the results...
obtained for patients with postoperative recurrent uterine cancer.9)

Needle applicator displacement is a problem associated with multifractionated HDR-ISBT; it causes a loss of dose conformity and may lead to unexpected marginal recurrence and/or complications. Although some studies, including ours, have investigated displacement in prostate Brachytherapy using CT images,10–17) few studies have involved patients with uterine cancer. Therefore, we evaluated daily CT images to examine flexible needle applicator displacement and reported the results obtained for patients with previously untreated uterine cervical cancer.18) In the present study, we reported the results of assessment of daily applicator displacement for postoperatively locally recurrent uterine cancer, and the role of corrective action.

MATERIALS AND METHODS

Patient and treatment characteristics

Between December 2009 and August 2010, 8 patients with 9 lesions of postoperative locally recurrent uterine cancer were treated by HDR-ISBT at the National Hospital Organization Osaka National Hospital using an ambulatory technique (Table 1). Primary site was 7 for uterine cervix and 1 for uterine corpus. Tumor locations included the vaginal stump with or without parametrium in 6 lesions and the vaginal wall in 3 lesions. No patient had distant metastatic lesions. The median gross tumor volume at the time of HDR-ISBT for each patient was 7.1 cc (0.9–197 cc).

Our treatment policy involved three treatment patterns. Patients with local recurrence within 2 years after previous surgery without a previous history of radiotherapy received combined EBRT and ISBT with or without concurrent chemotherapy. Four patients were included in this group. Patients with local recurrence after more than 2 years without a previous history of radiotherapy received ISBT as monotherapy at a dose of 54 Gy in 9 fractions per 5 days. One patient was included in this group. Patients with a previous history of radiotherapy received ISBT as monotherapy at a dose of 48 Gy in 8 fractions per 5 days. Three patients were included in this group; however, one patient received 49 Gy in 7 fractions per 5 days because there was a national holiday during the week. Four patients received EBRT to the whole pelvis (WP), with a median prescribed dose of 30 Gy in 1.8 or 2 Gy fractions each day (range, 30–45 Gy). After WP EBRT, center-shielded (CS) EBRT was administered (median, 20 Gy; range, 0–20 Gy). In principle, we administered ISBT at a dose of 30 Gy in 5 fractions per 3 days after WP EBRT and before CS EBRT. A midline block of CS EBRT was determined according to ISBT treatment volume. However, when CS EBRT was started before ISBT, we determined the extent of the midline block to cover the clinical target volume (CTV). We defined that CTV is same as the gross tumor volume.

Applicator implantation

Our unique implantation technique has been previously described in detail.7–9) We performed a single applicator implantation procedure with multiple fractions for all patients. Implantation was monitored by performing TRUS using SSD-1000® and ProSound Alpha 7® (Aloka Co. Ltd., Tokyo, Japan), and we adopted 11–23 (median 14) flexible needles (ProGuide Sharp Needle®; Nucletron, Veenendaal, The Netherlands). A single flexible needle applicator was inserted into the center of the vaginal stump (Fig. 1a). After implanting the first needle, a silicone cylinder was inserted

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Primary</th>
<th>Histology</th>
<th>Recurrence</th>
<th>Total gross Tumor volume</th>
<th>Irradiation history</th>
<th>Time interval after previous treatment</th>
<th>External beam radiotherapy</th>
<th>Interstitial brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>cervix</td>
<td>SCC</td>
<td>Vagina</td>
<td>11.6 cc</td>
<td>+</td>
<td>10 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>cervix</td>
<td>SCC</td>
<td>Stump/pm</td>
<td>7.9 cc</td>
<td>+</td>
<td>6 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>cervix</td>
<td>1Ad</td>
<td>Vagina</td>
<td>6.8 cc</td>
<td>+</td>
<td>57 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>cervix</td>
<td>SCC</td>
<td>Vagina, stump/pm</td>
<td>2.8 cc, 21.1 cc</td>
<td>–</td>
<td>3 months</td>
<td>45 Gy/25 fr.</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>cervix</td>
<td>SCC</td>
<td>Stump/pm</td>
<td>3.2 cc</td>
<td>–</td>
<td>15 months</td>
<td>30 Gy/15 fr.</td>
<td>20 Gy/10 fr.</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>endometrium</td>
<td>Ad</td>
<td>Stump/pm</td>
<td>7.1 cc</td>
<td>–</td>
<td>13 months</td>
<td>30 Gy/15 fr.</td>
<td>20 Gy/10 fr.</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>cervix</td>
<td>SCC</td>
<td>Stump/pm</td>
<td>0.9 cc</td>
<td>–</td>
<td>2 months</td>
<td>30 Gy/15 fr.</td>
<td>20 Gy/10 fr.</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>cervix</td>
<td>SCC</td>
<td>Stump/pm</td>
<td>197 cc</td>
<td>–</td>
<td>33 months</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*S: squamous cell carcinoma
†fr.: fractions
‡pm: parametrium
§Ad: adenocarcinoma
into the vagina (Fig. 1b). The cylinder had 5 implant holes, and the center hole was used for the first needle. After inserting the cylinder, we attached a custom-made vinyl plate to the patient’s perineum with holes for needle implantation. The vinyl plate had 5 holes for cylinder-guided implantation (Cylinder group) and several additional holes for free-hand implantation (Perineum group) (Fig. 1c).

We implanted the needle applicators in and around CTV with TRUS guidance, and beyond CTV to be able to correct dwell positions if the needle applicator was displaced caudally.

Treatment planning and treatment
All patients underwent CT and MRI after implantation, and CT-based planning was performed using MRI as a reference to draw the contour of CTV. CTV was delineated with the assistance of axial T2-weighted MR images. Treatment planning was performed using Plato® and Oncentra® brachy (Nucletron, Veenendaal, The Netherlands) with manual modifications. We used computer optimization (geometrical optimization) at first and modified the dwell times by manual to cover CTV adequately without excessive doses for organs at risk. We tried to cover CTV by prescribed isodose line. However, we compromised if excessive doses would be delivered to organs at risk. In such cases, our goal of dose specification was that the dose that covered 90% of CTV (D90(CTV)) must be more than the prescribed dose. We used microSelectron-HDR® (Nucletron) with an 192 Ir source.

Applicator displacement
Displacement measuring method has been previously described in detail. To measure flexible needle applicator displacement between fractions, we took CT images approximately 21, 45, 69, and 93 hours after implantation, i.e., after the second, fourth, sixth, and eighth treatment fractions. CT images with a thickness of 3 mm and pitch of 3 mm were obtained using Xvision TM/SP® (Toshiba Medical Systems Corporation, Tochigi, Japan). We loaded the images in Plato® and Oncentra® brachy obtained the relative coordinates of the 3 titanium markers and needle applicators. The needle applicator tips were identified by locating the end of the air column for each needle on the CT image;—this calculation method was similar to that of Kim et al.. We used the center of gravity of the 3 markers for reference. We calculated the distance between the needle tip and the center of gravity and compared it with the distance on the day of implantation and for several particular times after implantation. A positive value indicated that the needle displaced caudally and a negative value indicated that it displaced cranially.

The treatment plan was corrected on the basis of displacement. We changed each needle applicator length to its initial length plus or minus the displacement value. This moved dwell positions of the treatment source parallel to the needle applicator in order to achieve the same treatment position as that on the day of implantation. However, displacement of less than or equal to 3 mm was disregarded because the sec-
tion thickness of the CT image was 3 mm. Correction was performed only for the third, fifth, seventh, and ninth fractions because CT and evaluation of displacement were performed after the second, fourth, sixth, and eighth fractions.

Analysis

Dose–volume analysis was performed using a dose–volume histogram (DVH) and D90(CTV) was calculated. We used CTV data obtained on the day of implantation for DVH calculation because CTV obtained on that day was determined by CT and MRI, whereas CTV data obtained on the other days was determined by only CT without MRI. And so, we used CT on the other days only for measuring displacement distance in this analysis and input these data into the CT taken on the day of implantation (Fig. 2a, b). Statistical calculations were performed using Statview. The results of daily displacement and those of the implanted positions were compared. P values were obtained using the Mann–Whitney method. P < 0.05 was considered significant.

RESULTS

All 8 patients completed their treatment safely without any complications of needle applicator fixation. Median caudal needle applicator displacement was 3 mm (range, −4 to 16 mm) at the first 21 hours, 2 mm (range, −7 to 19 mm) at 45 hours, 4 mm (range, −2 to 23 mm) at 69 hours, and 5 mm (range, −2 to 26 mm) at 93 hours (Fig. 3). Significant caudal displacement was observed between 0 and all other periods (P < 0.0001). Significant differences were also observed between 21 and 93 hours (P < 0.01) and 45 and 93 hours (P < 0.01). Of the 122 applicators, more than 15 mm displacement was observed for 2 of 122 needles (2%) at 21 hours, 7 of 110 needles (6%) at 45 hours, 6 of 60 needles (10%) at 69 hours, and 10 of 60 needles (17%) at 93 hours. More than 10 mm displacement was observed for 26 of 122 needles (21%) at 21 hours, 29 of 110 needles (26%) at 45 hours, 18 of 60 needles (30%) at 69 hours, and 19 of 60 needles (32%) at 93 hours.

We compared needle applicator displacements between the Cylinder and Perineum groups (Fig. 4). In the Cylinder group, median needle applicator displacement was 1 mm (range, −4 to 16 mm) at the first 21 hours, 1 mm (range, −5 to 16 mm) at 45 hours, 2.5 mm (range, −2 to 12 mm) at 69 hours, and 2.5 mm (range, −2 to 13 mm) at 93 hours. On the other hand, in the Perineum group, median needle applicator displacement was 5 mm (range, −3 to 14 mm) at the first 21 hours, 5 mm (range, −7 to 19 mm) at 45 hours, 6.5 mm (range, −2 to 23 mm) at 69 hours, and 7 mm (range, −1 to 26 mm) at 93 hours. Significant differences were observed between the 2 groups throughout the treatment period.

We investigated needle applicator displacement in each patient. When the median value of displacement was evalu-
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Rated for each patient, more than 10 mm displacement was observed in 2 of 8 patients (25%).

The DVH values without corrective action were investigated. D90(CTV) without corrective action is shown in Fig. 5. Two of 8 patients showed more than 10% reduction in D90(CTV) values compared with the initial treatment plan of which 1 patient showed a deviation at 21 hours and the other at 69 hours. D90(CTV) with corrective action was improved to 98–100% of the result of the first day.

DISCUSSION

ISBT has been selected as a good treatment option for postoperative recurrent uterine cancer. However, applicator displacement is a critical issue for multifractionated schedule, and has been mainly discussed for prostate cancer.10–17 Hoskin et al. reported that the mean displacement of catheters between fractions was 11.5 mm (range, 0–42 mm),10 while Kim et al. reported a mean displacement of 5.5 mm (range, −3.8 to 8.0 mm)11 using a precise CT method. We have reported an average displacement of 7 mm at 69 hours in prostate HDR-ISBT15 using a CT method.

On the basis of our prostate ISBT experience, we initially decided dwell positions for the treatment source to cover CTV with a 15-mm cranial margin.15,18 Furthermore, we corrected the dwell positions by the daily CT method. We also investigated the procedure for previously untreated uterine cervical cancer and reported a median displacement of 2 mm at 45 hours after implantation,18 which is smaller than that observed with the procedure for prostate cancer.15

In the present study, median caudal needle applicator displacement in postoperative recurrent uterine cancer was 3 mm (range, −4 to 16 mm) at the first 21 hours, 2 mm (range, −7 to 19 mm) at 45 hours, 4 mm (range, −2 to 23 mm) at 69 hours, and 5 mm (range, −2 to 26 mm) at 93 hours. More than 15 mm displacement was observed for 2 of 122 needles (2%) at 21 hours, 7 of 110 needles (6%) at 45 hours, 6 of 60 needles (10%) at 69 hours, and 10 of 60 needles (17%) at 93 hours. From these results, a cranial margin of 15 mm became unsatisfactory for treatments longer than 45 hours after implantation in cases where no displacement adjustment was achieved.

Hoskin et al. identified one of the causes of displacement in prostate brachytherapy as tissue edema.10 We agree that tissue edema is a major concern with our ambulatory technique for pelvic brachytherapy.18 In previously untreated uterine cervical cancer, we reported that displacement in the Perineum group (median, 3 mm at 45 hours) was significantly greater than that in the Cylinder group (median, 1 mm at 45 hours). In the Cylinder group, the caudal half of the needle applicator was placed in the silicone cylinder in the vaginal cavity, while the cranial half was directly implanted in the tissue (mainly the uterine cervix and tumor lesion). In the Perineum group, the entire needle applicator was inserted into the tissue (skin, subdermal/paracervical tissue, and tumor lesion), suggesting that perineal tissue edema occurred more frequently in the Perineum group.

The influence of tissue edema seems to be important in postoperative recurrent uterine cancer similar to that in previously untreated uterine cervical cancer. In the Cylinder group, median needle applicator displacement was 1, 1, 2.5, and 2.5 mm at 21, 45, 69, and 93 hours, respectively. In Perineum group, median needle applicator displacement was 5, 5, 6.5, and 7 mm at 21, 45, 69, and 93 hours, respectively.

Some authors have reported improvements in DVH results in prostate brachytherapy by corrective action.10,12–14,16,17 Simnor et al. obtained CT images before every treatment session and used corrective action14 if displacement was
more than 5 mm. The D90% value improved from −28% without correction to −5% with correction between first and second fractions (afternoon of day 1 and morning of day 2). Our method concurred with their protocol, but we used corrective action if displacement was more than 3 mm because the thickness of the CT image was 3 mm. Our DVH result showed that 2 of 8 patients showed more than 10% reduction in the D90(CTV) value. Such a reduction in D90(CTV) is not negligible and may lead to unexpected marginal recurrence. In previously untreated cases, high risk CTV includes the normal uterine cervical tissue. In contrast, CTV in post-operative recurrent cases includes less normal tissues. Thus, we consider reduction in D90(CTV) is important in postoperative locally recurrent uterine cancer.

In summary, we investigated needle applicator displacement with our ambulatory technique and daily CT scans in patients with postoperative recurrent uterine cervical cancer. A cranial margin of 15 mm is not satisfactory for multifractionated HDR-ISBT longer than 45 hours after implantation. Correction of the treatment source improves treatment DVH for multifractionated HDR-ISBT.

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