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# Dosimetric impact of rotational setup errors in volumetric modulated arc therapy for postoperative cervical cancer

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## ABSTRACT

We aimed to evaluate the impact of rotational setup errors on the doses received during postoperative volumetric-modulated arc therapy (VMAT) for cervical cancer. Overall, 121 cone-beam computed tomography (CBCT) sets from 20 patients were rigidly registered to reference computed tomography (CT) sets based on bony landmarks. The rotational setup errors (pitch, yaw and roll) were calculated. Then, 121 CT sets involving rotational setup errors were created, and the dose distribution in these CT sets were recalculated. The recalculated dosimetric parameters for the clinical target volume (CTV) and organs at risk (OAR) were compared to the reference values, and the correlation coefficients between the dosimetric parameter differences and rotational setup errors were calculated. Only the pitch setup error was moderately correlated with CTV coverage ($r \geq 0.40$) and strongly correlated with V45 for the bladder ($r \geq 0.91$) and V40 for the rectum, small bowel and bone marrow ($r \geq 0.91$). The maximum dosimetric difference in a single fraction and overall fractions was −1.59% and −0.69% in D98 for the CTV, 11.72% and 5.17% in V45 for the bladder and −8.03% and −4.68% in V40 for the rectum, respectively. In conclusion, rotational setup errors only slightly impact dose coverage during postoperative cervical cancer VMAT. However, the pitch setup error occasionally affected the doses received by the bladder or the rectum in the overall fraction when the error was systematic. Thus, rotational setup errors should be corrected by adjusting six-degree-of-freedom (DOF) couches to reduce dosimetric differences in the OARs.

**Keywords:** residual rotational setup error; dosimetric impact; postoperative cervical cancer; volumetric-modulated arc therapy (VMAT); image-guided radiation therapy (IGRT)

## INTRODUCTION

Intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) can involve complex dose distributions (e.g. convex and concave shapes). Such irradiation techniques have enhanced the doses received by targets and reduced those received by normal tissues in many treatment sites, including the prostate and head and neck [1,2]. IMRT is reported to reduce the doses received by the bladder, rectum and small bowel during adjuvant radiotherapy after radical hysterectomy for cervical cancer treatment [3]. However, daily interfractional setup errors may cause lower dose distribution on the target and higher dose distribution on the organs at risk (OARs) because of the widely defined target.

With regard to the dosimetric impact of rotational setup errors, Amro *et al.* reported that prostate rotations can cause significant underdosing even if daily translations are managed [4]. Jiang *et al.* also demonstrated that rotational setup errors can lead to insufficient dose to the target volume and increase in the spinal cord dose in IMRT for primary malignant tumor of the cervical spine [5]. In addition, Guckenberger *et al.* highlighted the clinical significance of rotational errors for select patients with elongated, non-spherical target volumes

and sharp dose gradients between the target organs and adjacent OARs [6].

Rotational setup errors in gynecological cancers may affect the doses received by the target and OARs because the targets are typically elongated and adjacent to the OARs. Weiss *et al.* evaluated the rotational setup errors with an electronic portal imaging device and an infrared body marker-based system [7]. Several studies have shown that rotational setup errors can occur with various imaging devices including in cone-beam computed tomography (CBCT) [8], megavoltage CT [9] and orthogonal kilovoltage X-ray imaging [10]. However, few studies have investigated the impact of rotational setup errors on the doses received by the target and normal tissues in patients with gynecological cancer. Yao *et al.* reported that the margin sizes calculated for translational and rotational setup errors influenced the OARs in postoperative cervical cancer treatment [11]. However, the direct influence of rotational setup errors on the doses received by the target and OARs was not demonstrated. Zhang *et al.* evaluated the dosimetric changes of target coverage by translational and rotational setup errors in definitive cervical cancer treatment [12]. However, the influence of translational and rotational setup errors on the doses received by the OARs was not demonstrated.

Thus, the present study aimed to evaluate the dosimetric impact of rotational setup errors on the doses received during postoperative VMAT for cervical cancer. Toward this goal, interfractional rotational setup errors were analyzed, and the correlations between the target and OAR dose differences and rotational setup errors were calculated. Then, the influence of rotational setup errors on the doses received by the target and OARs were evaluated for individual patients. Interfractional motions and deformations of the target and normal tissues were not considered. The target and normal tissues in most patients could not be contoured because of the limited imaging range of CBCT and its insufficient image quality.

## MATERIALS AND METHODS

### Study design and patients

This retrospective study was approved by the appropriate institutional review board on 27 October 2015 (approval number: 1510279150). All patients provided written informed consent to participate in the study.

The subjects were 20 consecutive patients with stage IB1-IIB cervical cancer (International Federation of Gynecology and Obstetrics) who were treated with adjuvant radiotherapy after radical hysterectomy between June 2013 and March 2015 at our institute. Of these, 12 patients underwent concurrent chemoradiotherapy, whereas eight received radiotherapy alone. Eleven patients also underwent ovary transposition to reduce scatter from the radiation field to the ovaries. The patient characteristics are summarized in Table 1.

**Table 1. Patient characteristics. Field length was defined as the distance between the collimator jaws in the cranio-caudal direction**

| | *n* |
|---|---|
| Total patients | 20 |
| Age (years) | |
| Median (range) | 42 (31–70) |
| Histology | |
| Squamous cell carcinoma | 16 |
| Adenocarcinoma | 4 |
| FIGO Stage | |
| IB1 | 9 |
| IB2 | 7 |
| IIA | 1 |
| IIA1 | 1 |
| IIA2 | 1 |
| IIB | 1 |
| Surgery | |
| Radical hysterectomy | 20 |
| Adjuvant Treatment | |
| Concurrent chemoradiotherapy | 12 |
| Radiotherapy alone | 8 |
| Ovary transposition (patients) | |
| Bilateral | 10 |
| Left only (right resected) | 1 |
| VMAT technique | |
| Two-arc | 17 |
| Four-arc | 3 |
| Field length (cm) | |
| Median (range) | 23.45 (19–26.5) |
| CTV (cc) | |
| Median (range) | 435.15 (289.8–614.4) |
| Bladder volume (cc) | |
| Median (range) | 255.9 (67.4–589.4) |

*Abbreviations:* VMAT = volumetric-modulated arc therapy; CTV = clinical target volume

### Treatment planning and image-guided radiation therapy protocol

Each patient underwent CT using Lightspeed 16 (GE Healthcare, UK). These reference CT sets were acquired with 2.5-mm-thick slices after the bladder was filled for 1 hour. No instruction regarding rectum filling was given. Each patient was placed in the supine position and immobilized using HipFix (CIVCO Medical Solutions, USA), Moldcare (ALCARE Co., Ltd., Japan) and a foot support. The markers were drawn on the patient's skin (vertically, longitudinally and laterally) and on the Moldcare (longitudinally).

The CTV included the parametrium, iliac lymph nodes (common, internal and external), and presacral lymph nodes. The lymph node region was defined as an area enclosed by a 7 mm margin around the relevant pelvic vessels, not including the bones and muscles, as specified by Toita *et al.* [13]. The planning target volume (PTV) was defined by a uniform margin of 5 mm outside the CTV. The bladder, rectum, small bowel, large bowel, bone marrow and ovaries were contoured as the OARs. The rectum was contoured from the inferior aspect of the third sacral vertebra to the anal verge. The pelvic bone, lumbar vertebrae from the superior aspect of the PTV and femoral head were delineated as surrogates for the bone marrow.

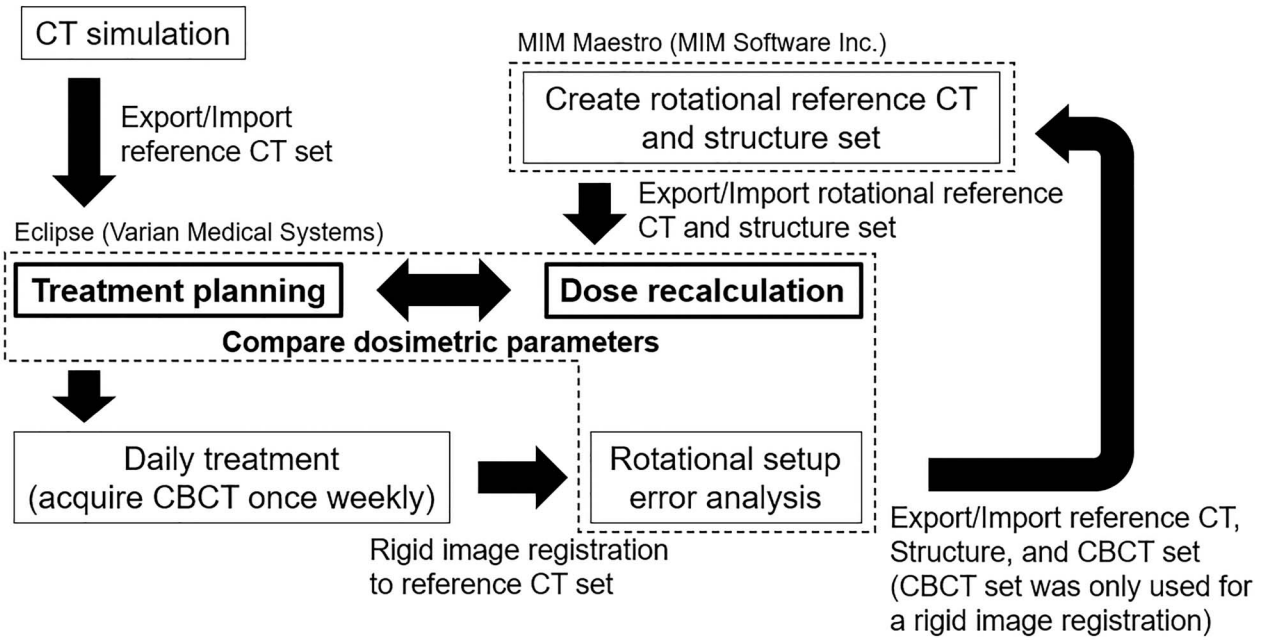


**Fig. 1. Procedure flowchart of the rotational setup error analysis and dose recalculation.**

The prescription dose to 95% of the PTV was 50.4 Gy, which was delivered in 28 fractions using two- or four-arc VMAT. Since November 2014, the four-arc technique has been employed at our institute to protect the ovaries from scattered radiation [14]. The detail of this technique was that two arcs turned off the beam to avoid irradiating the ovaries directly when an ovary overlapped the PTV in the beam's eye view, and the remaining two arcs irradiated the lower PTV inferior to the ovaries to increase the conformity of the lower PTV. The dose constraints of the OARs were based on the Radiation Therapy Oncology Group 1203 trial guidelines as follows: the bladder volume receiving 45 Gy (V45) should be 35% at most; the rectal volume receiving 40 Gy (V40) should be 80% at most; V40 for the small bowel should be 30% at most; V40 for the large bowel should be 80% at most; and the bone marrow volume receiving 10 Gy (V10) and V40 should be 90% and 37%, respectively, at most [15]. Per the institutional protocol, the maximum dose (Dmax) to the ovary should be 6 Gy, and the volume receiving 3 Gy (V3) should be as low as possible. Dose constraints to prevent side effects were determined based on the literature [16,17]. All dose calculations were performed using Anisotropic Analytical Algorithm in Eclipse ver. 11.0.47 (Varian Medical Systems, USA), and the center of the mass of the PTV was defined as the isocenter.

Each patient was irradiated using a Clinac 23EX (Varian) implemented Exact Couch (Varian), which is a four-degree-of-freedom (DOF) couch and a 6-MV photon beam. First, the patient was aligned using skin markers, the Moldcare immobilizing brace, and a room laser. Second, orthogonal kilovoltage X-ray image guidance was performed in each session using On-Board Imager (Varian). CBCT images were also acquired once weekly after orthogonal imaging. Both X-ray and CBCT image guidance corrected only the translational setup errors because Exact Couch cannot correct the pitch and roll setup errors.

## Rotational setup error analysis

The procedure flowchart of the present study is illustrated in Fig. 1. Six to seven CBCT sets were obtained per patient. In total, 121 CBCT sets were registered to reference the CT sets based on the bony landmarks (from the upper rim of the fourth lumbar vertebra to the top of the pelvic bone). This was done by employing a rigid image registration application (Eclipse, Varian) using the downhill simplex method and mutual information. Automatic rigid image registration was performed thrice while reducing the resolution size. All rigid image registrations were verified manually after automatic image registration. The residual rotational setup errors (pitch, yaw and roll) were still present after the image guidance procedure were calculated. Pitch was defined as a rotation around the right-to-left axis through the isocenter, yaw was defined as a rotation around the anterior-to-posterior axis through the isocenter, and roll was defined as a rotation around the superior-to-inferior axis through the isocenter. The positive directions were defined as raising the head and lowering the feet for pitch, moving the head to the right for yaw and lifting the right side and lowering the left for roll, as illustrated in Fig. 2a, b and c. The mean and standard deviation (SD) rotational setup errors were calculated as the averages and SDs of the absolute rotational setup errors for individual patients.

## Dose recalculation on the rotational reference CT set

The reference CT, structure sets and CBCT sets were imported from Eclipse into MIM Maestro ver. 6.6.12 (MIM Software Inc., USA) in DICOM format. Then, the reference CT sets were registered with the CBCT sets, and the calculated rotational setup errors were manually substituted. In total, 121 rotational reference CT sets and structure

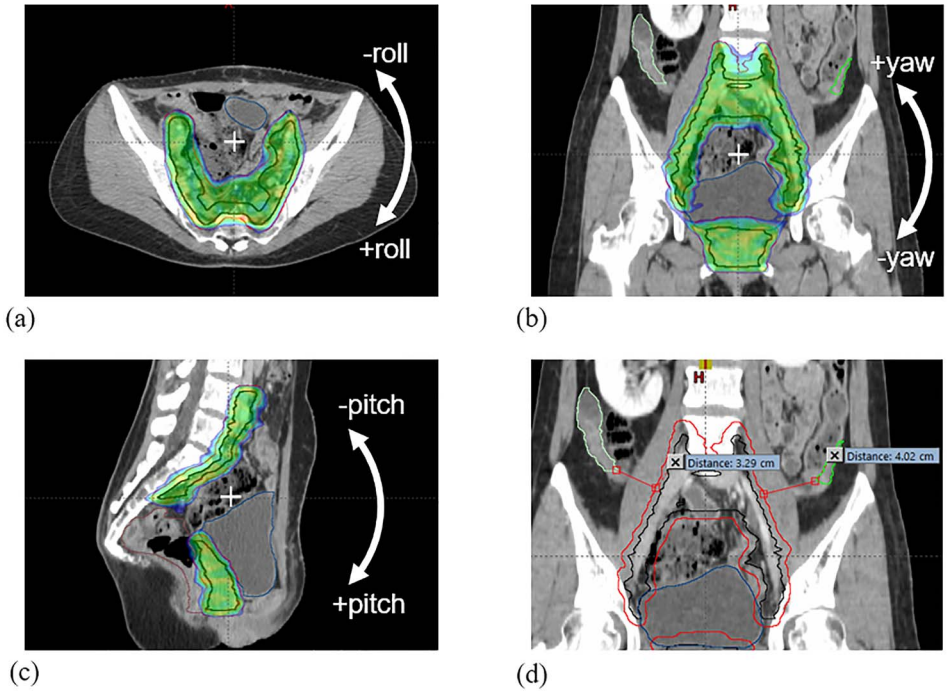


**Fig. 2. (a), (b) and (c) Treatment planning during postoperative VMAT for cervical cancer, on the axial, coronal and sagittal planes. The contouring of the CTV, PTV, bladder and rectum are illustrated as black, red, blue and brown lines, respectively. The color wash is shown as the prescription dose to 95% of the PTV. The isocenter is indicated by a cross. The positive and negative directions of the rotational setup errors are shown on each plane. (d) The measurement of the minimum distance between the ovaries (green and light green lines) and the PTV surface, using a scaling tool on the coronal plane**

sets involving the calculated rotational setup errors were created. MIM Maestro was used to create these rotational reference CT sets and structure sets because of the unavailability of Eclipse. Dose distributions were recalculated on these CT sets with Eclipse using the same beam parameters as in the treatment plans. All structure volumes in the rotational reference CT sets were compared with reference structure volumes to ensure the accuracy of the creations.

## Evaluation of dosimetric impact of rotational setup errors

The recalculated and reference dosimetric parameters were then compared, defining the difference of each dosimetric parameter as the recalculated dosimetric parameter minus the reference value. For the CTV, the D2 (near-maximum dose), D95, D98 (near-minimum dose), Paddick's conformity index (CI) and homogeneity index (HI) were calculated as the dosimetric parameters representing the target coverage [18,19]. The CT and HI are defined using the following formulae:

$$CI = \frac{TV_P}{TV} \times \frac{TV_P}{V_P} \times 100\%$$

where TVP is the target volume covered by the prescription dose, TV is target volume and VP is volume of the prescription dose.

$$HI = \frac{D_2 - D_{98}}{D_P} \times 100\%$$

where DP is the prescription dose.

For the OARs, we calculated the V45 for the bladder; V40 for the rectum, small bowel and large bowel; V10 and V40 for the bone marrow; and Dmax and V3 for the ovaries. The correlation coefficients between the dosimetric parameter differences and rotational setup errors were calculated. In addition, for the ovaries, the correlation between the dosimetric parameters and minimum distance from the PTV surface was evaluated for each VMAT technique. The minimum distance from the PTV surface was measured with a scaling tool within Eclipse, observing the contours of the ovaries and PTVs on all coronal planes, as illustrated in Fig. 2d.

Moreover, six to seven CBCT sets per patient were assumed to be a representative sample of the 28 fractions. Averaging the six to seven fractional dosimetric parameter differences per patient, the dosimetric parameter differences in the overall fraction were evaluated per patient.

## RESULTS

The rotational setup errors for the three axes in all fractions for all patients are illustrated in Fig. 3. The mean ± SD of the pitch, yaw and roll setup errors were 0.88° ± 0.64°, 0.42° ± 0.38° and 0.36° ± 0.26°, respectively. The maximum pitch, yaw and roll setup errors were 3.90°,

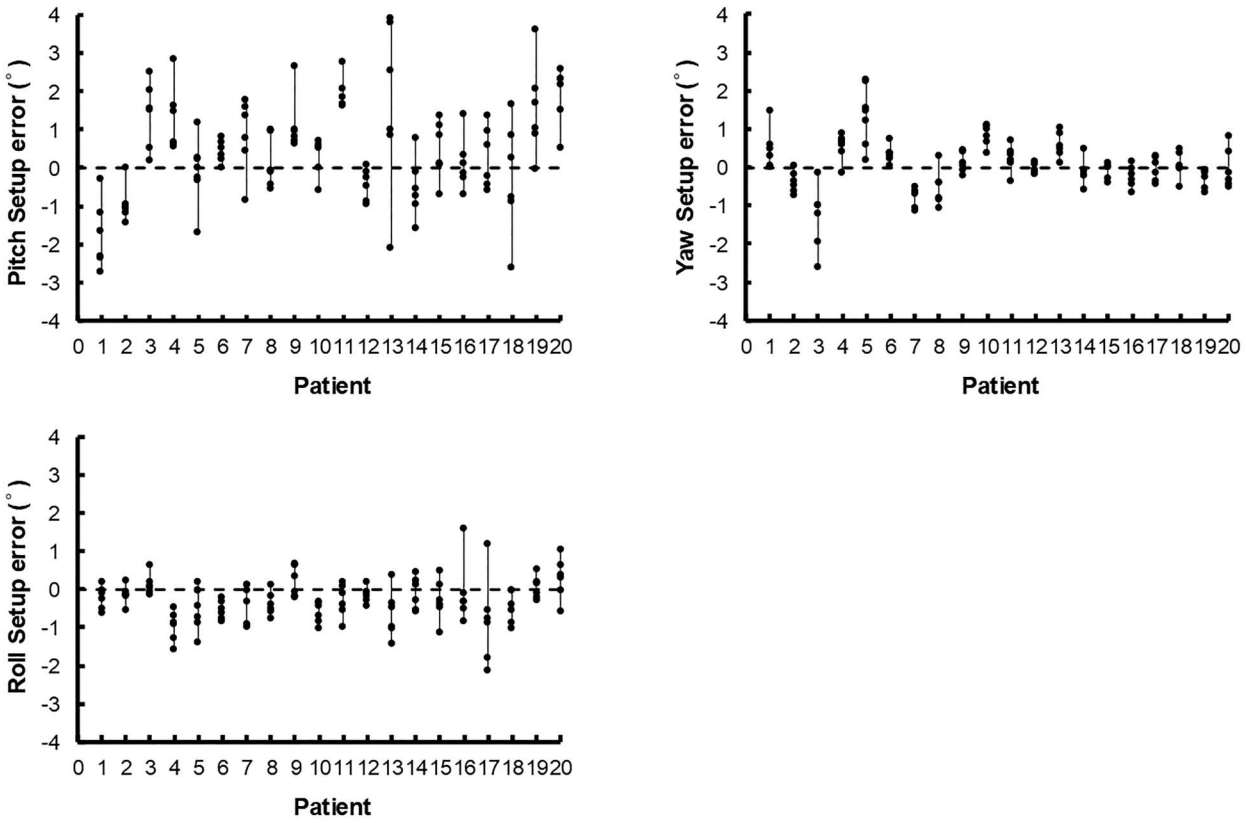


**Fig. 3. Rotational setup errors with respect to three axes in all fractions for each of the 20 patients. The pitch setup error is considerable compared to the yaw and roll setup errors.**

−2.61° and −2.13°, respectively. The pitch setup error was considerably larger than the yaw and roll setup errors.

All volume differences between the reference and rotational structure sets were either less than 1% or 1 cc for all the structures, indicating that the rotational reference CT and structure sets were created accurately. Only the pitch setup error was found to be strongly correlated with D2, D95 and D98 differences for the CTV, as illustrated in Fig. 4a. In addition, only the pitch setup error was found to be moderately correlated with the CI and HI differences for the CTV. Fig. 4b and c depict the correlations for the yaw and roll setup errors, respectively. All correlation coefficients for the CTV are summarized in Table 2. The maximum difference was −1.59% for D98 in a single fraction.

Similarly, only the pitch setup error was found to be strongly correlated with the difference in V45 for the bladder (Fig. 5a), with a correlation coefficient of 0.91. The maximum difference was 11.72% in a single fraction, corresponding to a pitch setup error of 2.81°. However, the yaw and roll setup errors were not correlated with the difference in V45 for the bladder (Fig. 5b and c).

The differences in V40 for the rectum, small bowel and bone marrow were also found to be strongly correlated with the pitch setup error. In contrast, the differences in almost all the OAR parameters (except in V40 for the large bowel) were not correlated with the yaw and roll setup errors (Table 2). The correlations between V40 for the rectum and the rotational setup errors were similar to those of V45 for the bladder.

The minimum distance from the PTV surface was strongly correlated with the reference value of Dmax for the ovaries in both VMAT techniques (Fig. 6a). Furthermore, the reference values of V3 for the ovaries were also moderately or strongly correlated with the minimum distance in both VMAT techniques (Fig. 6b). The mean ± SD of the reference value for Dmax and V3 for the ovaries in the two-arc VMAT were 8.08 ± 2.78 Gy and 83.42 ± 30.84%, respectively. However, the mean ± SD of the reference value of Dmax and V3 for the ovaries in the four-arc VMAT were 5.34 ± 1.91 Gy and 49.83 ± 23.19%, respectively. The dose received by the ovaries was lower when the four-arc was used compared to that when the two-arc VMAT technique was used. Rotational setup errors caused the Dmax and V3 for the ovaries to change by a maximum of 5.33 Gy and 9.20%, respectively, in a single fraction.

The differences in the overall dosimetric parameters for all patients are summarized in Table 3. The maximum overall differences in the CTV were −0.32% for D2, −0.60% for D95, −0.69% for D98, 0.76 for CI and 0.51 for HI. Similarly, the maximum overall differences in the large bowel and the bone marrow were −0.96% for V40 and −0.71% for V40, respectively. However, the maximum overall differences in the other OARs were 5.17% in V45 for the bladder (patient #20), −4.68% in V40 for the rectum (patient #3), −3.40% in V40 for the small bowel (patient #20), 3.56 Gy in Dmax for the ovary (patient #11), and −3.91% in V3 for the ovary (patient #5). Only the overall

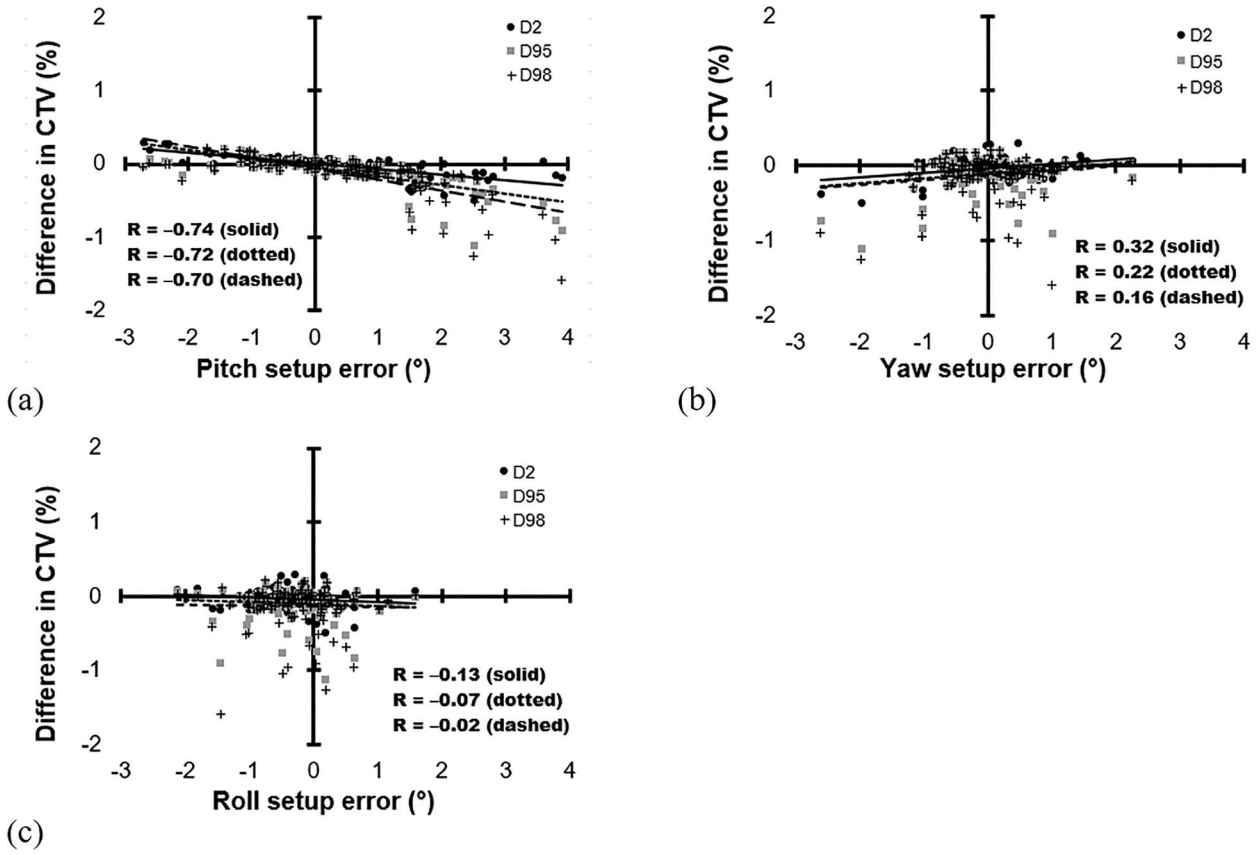


**Fig. 4. Correlations between the differences in D2 (circles), D95 (squares) and D98 (crosses) in the CTV and the (a) pitch, (b) yaw and (c) roll setup errors. The solid, dotted and dashed lines represent the linear regression lines for D2, D95 and D98, respectively.**

dosimetric parameter differences in V3 for 9 ovaries were zero. All these ovary volumes received more than 3 Gy (i.e. V3 was 100%) (Fig. 6b).

## DISCUSSION

The direct impact of the rotational setup errors on the doses received by the target and OARs in those with cervical cancer during post-operative VMAT is unclear. This study found four major findings. First, the pitch setup error was considerably larger than the yaw and roll setup errors, consistent with the results of previous studies on the pelvic region [6,8,10,20–22]. Recent reports have shown that this difference is caused by the relative difficulty in aligning longitudinal skin markers, compared to aligning vertical and lateral skin markers, in the pelvic region using room lasers [8,20]. Our results agree with this conclusion. Moreover, the shape of the pelvis and the amount of subcutaneous fat vary with sex. The female pelvis is oval and broader than the male pelvis, which is taller and narrower; therefore, the larger pitch setup error may be caused by the instability of the female pelvis in the superior-to-inferior direction. Furthermore, fat content is higher in females than in males. Laaksomaa *et al.* reported that the tattoo marks used for patient positioning in female patients shifted in a direction different from that seen in male patients [10]. In addition, Ahmad *et al.* reported that the pitch setup error was moderately correlated with the different filling of the bladder in the prone position, in locally advanced cervical cancer patients [23]. They explained that the patients were probably uncomfortable with the pressure on their belly, with a full bladder; the patients then adjusted their pelvis orientation to release the pressure. With reference to their report, the larger pitch setup error may be caused by differences in filling of the bladder or the rectum in the supine position. In particular, no instruction regarding rectum filling was provided in the present study.

Second, only the pitch setup error was strongly correlated with D2, D95 and D98 ($r \geq 0.70$) and moderately correlated with CI and HI ($r \geq 0.40$) for the CTV. Only the pitch setup error was strongly correlated with several dosimetric OAR parameters ($r \geq 0.91$), i.e. V45 for the bladder and V40 for the rectum, small bowel and bone marrow. Meanwhile, V40 for the large bowel, V10 for the bone marrow and Dmax and V3 for the ovaries were only weakly correlated with the pitch setup error. The large bowel is close to the isocenter, and most of the bone marrow volume received a low radiation dose of 10 Gy. Consequently, these two OARs were only slightly affected by rotational setup errors. The ovary parameters may be strongly affected by factors other than rotational setup errors, as discussed below. In contrast, there

**Table 2. Differences in dosimetric parameters and their correlation coefficients with the rotational setup errors**

| | | Difference | | Correlation coefficient | | |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Range | Pitch | Yaw | Roll |
| CTV | D2 (%) | −0.04 ± 0.13 | −0.50–0.30 | −0.74 | 0.32 | −0.13 |
| | D95 (%) | −0.10 ± 0.21 | −1.12–0.21 | −0.72 | 0.22 | −0.07 |
| | D98 (%) | −0.13 ± 0.28 | −1.59–0.21 | −0.70 | 0.16 | −0.02 |
| | CI | 0.35 ± 0.24 | −0.61–0.93 | 0.40 | −0.17 | 0.06 |
| | HI | −0.10 ± 0.22 | −0.09–1.41 | 0.47 | −0.01 | −0.05 |
| Bladder | V45 (%) | 1.17 ± 2.54 | −5.17–11.72 | 0.91 | 0.01 | −0.03 |
| Rectum | V40 (%) | −0.92 ± 2.61 | −8.03–6.19 | −0.91 | 0.12 | −0.07 |
| Small bowel | V40 (%) | −0.42 ± 1.51 | −4.90–3.06 | −0.91 | 0.11 | −0.18 |
| Large bowel | V40 (%) | 0.03 ± 0.43 | −1.69–0.91 | −0.30 | 0.26 | 0.03 |
| Bone marrow | V40 (%) | 0.15 ± 0.55 | −1.10–1.57 | 0.95 | −0.05 | 0.00 |
| | V10 (%) | 0.07 ± 0.17 | −0.32–0.70 | 0.39 | −0.03 | −0.05 |
| Ovary (two-arc) | Dmax (Gy) | 0.99 ± 1.52 | −0.59–5.33 | 0.46 | −0.05 | −0.15 |
| | V3 (%) | 0.30 ± 2.17 | −6.11–9.20 | 0.36 | −0.18 | 0.17 |
| Ovary (four-arc) | Dmax (Gy) | 0.11 ± 0.34 | −0.52–1.48 | −0.29 | −0.29 | 0.12 |
| | V3 (%) | 0.81 ± 2.45 | −5.77–5.29 | 0.15 | 0.11 | −0.19 |

*Abbreviations:* CTV = clinical target volume; D2, D95 and D98 = minimum doses received in 2%, 95% and 98% of the volume, respectively; CI = Paddick's conformity index; HI = homogeneity index; Dmax = maximum dose; V45, V40, V10 and V3 = volumes receiving 45 Gy, 40 Gy, 10 Gy and 3 Gy, respectively.

were no correlations between the yaw and roll setup errors and almost all dosimetric parameters because almost all OARs, except the ovaries, were arranged on the anterior or posterior side of the CTV.

Third, rotational setup errors slightly affected CTV coverage in a single fraction, despite the CTV being elongated. In contrast, only the pitch setup error considerably affected the single fractional doses received by the bladder, rectum and small bowel because these organs overlapped the PTV, which was the high-dose region. Fu *et al.* concluded that the rotational setup errors introduce minor dosimetric influence on IMRT targets for head and neck cancer. However, a noticeable dose increase was observed for the spinal cord in some patients. They also concluded that the dosimetric influence of the rotational setup errors should be evaluated carefully, case by case when OARs are close to the target. Our results agree with those findings obtained by Fu *et al.* [24].

Moreover, the dosimetric parameter differences in the overall fraction in the CTV, large bowel and bone marrow were less than 1% for all patients. However, the overall differences in V45 for the bladder or V40 for the rectum were approximately 5% for three patients (patient #3, 4 and 20), despite the overall differences for most patients being approximately $\leq 3\%$. When the pitch setup error was systematic, the doses received by the bladder or rectum were noticeable. However, a set of Clinac 23EX and Exact Couch (Varian), which is a four-DOF couch, cannot measure the pitch and roll setup errors via online imaging. Murphy provided two rules for rotational offset management in cases where only translational offsets are corrected: (i) the registration landmarks should closely demarcate the targeted treatment site, and (ii) the rotational degrees of freedom should not be included in the rigid registration due to dependence on the relative locations of the registration landmarks, the treatment site and the rotational axes [25]. Therefore, in our institute, translation only registration was performed on pelvic bones close to the center of the treatment site. Rotational correction of a six-DOF couch can sufficiently reduce the dosimetric differences in targets and normal tissues. However, a six-DOF couch has the mechanical limit of 3°, so it may be necessary to perform a patient setup again if the rotational setup error of 3° or more occur. The translational setup errors of the bony landmarks may be used to indicate the rotational setup errors. For example, when the rotational setup error of 3° (tan 3°) is converted with the translational setup error, the translational setup error is 5.24 mm at an offset position of 10 cm from the isocenter.

Finally, Dmax for the ovaries in the two-arc VMAT were moderately correlated whereas V3 for the ovaries in the two-arc VMAT were weakly correlated with the pitch setup error. However, Dmax for the ovaries in the four-arc VMAT were weakly correlated whereas V3 for the ovaries in the four-arc VMAT were not correlated with the pitch setup error. These differences may be caused by the small number of ovaries (three patients in four-arc VMAT in the present study). The correlations between the dosimetric parameters and the minimum distance from the PTV surface were evaluated, and we found that this distance was strongly correlated with Dmax for the ovaries and moderately correlated with V3 for the ovaries. These results suggest that lateral ovary transposition should be performed to ensure that the ovaries are sufficiently distant from the PTV. Hwang *et al.* and Yoon *et al.* also recommended that the ovaries be sufficiently distant to preserve ovarian function. Hwang *et al.* recommended that The PTV should be more than 1.5 cm above the iliac crest [26,27].

Rotational setup errors influenced the ovarian dose in both single and overall fractions. The maximum difference in single fraction and the maximum overall difference was 5.33 Gy and 3.56 Gy for Dmax, respectively. Rotational setup errors should be considered to avoid underestimating the ovarian dose, although the planned ovarian dose in the present study is permissible (ovarian sterilizing dose of 14.3 Gy at 30 s) [17]. Nevertheless, the dose should be further reduced to 3 Gy

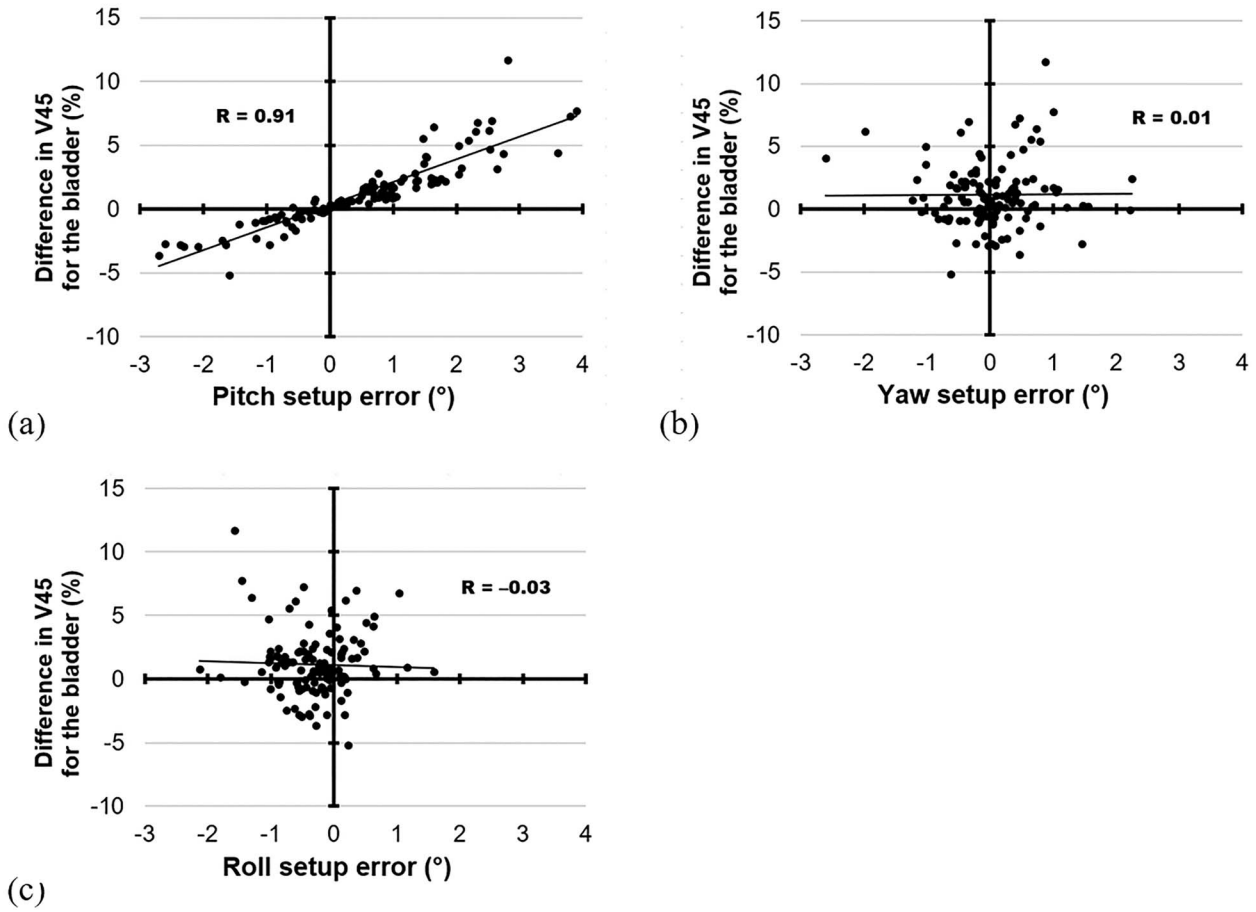


**Fig. 5. Correlations between the difference in V45 for the bladder and the (a) pitch, (b) yaw and (c) roll setup errors. The solid line represents a linear regression. Only the pitch setup error is strongly correlated with the difference in V45 for the bladder, and the maximum difference is 11.72%.**

to preserve ovarian function [16,28,29]. The dosimetric differences in V3 for nine ovaries were zero because the volume outside the ovary received 3 Gy. The doses received by the ovaries were lower in four-arc VMAT than in two-arc VMAT. However, it should be noted that scattered radiation from linac is not considered in the commercial treatment planning system. Kase *et al.* reported that scattered radiation contributes from 20% to 40% of the total dose outside a treatment field depending on the machine collimators, field size and distance from the field, whereas leakage radiation contributes very little to the total dose [30]. Qiu *et al.* reported that scattered doses from IMRT and VMAT are similar in magnitude, ranging from 100's of cGy near the field border to about 10 cGy 30 cm away in gynecological cancer patients by Mote Carlo simulation [31]. For example, the mean scattered dose for the kidney was estimated at 40 cGy. An IMRT leakage dose of approximately 6 cGy is uniformly distributed throughout the patient, while the leakage dose from VMAT is about 3 cGy due to the reduced number of monitor units.

A limitation of the present study was that interfractional motions, intrafractional motions and deformations of the target and normal tissues were not considered. The target and normal tissues in most patients could not be contoured because of the limited imaging range of CBCT and the insufficient image quality of CBCT. As described in International Commission on Radiation Units and Measurements Report 62, actual dose distribution should consider not only the setup error, but also the internal variations from movements of the bowel and different fillings of the bladder or the rectum [32]. Several studies have reported that variations in the rectal or bladder volume are correlated with significant displacement of the vagina and can cause the target coverage or OAR doses to change [33–37]. Jurgenliemk-Schulz *et al.* reported that the rectal volume difference of 100 cc caused the vaginal shift of 1 cm in the anterior-inferior direction [35]. Harris *et al.* also showed that the median interfractional vaginal motion is 5.8 mm (range, 0.6–20.2 mm) [38]. The results indicate that the dosimetric impact observed in the present study may be more substantial. Another limitation was the small number of ovaries included in the present study. Further studies are needed to evaluate the dosimetric impact of rotational setup errors on the ovaries. In addition, lumbar vertebra bending was not considered in the present study because the independent bending that occurs with pelvic rotation only slightly affects setup errors [22].

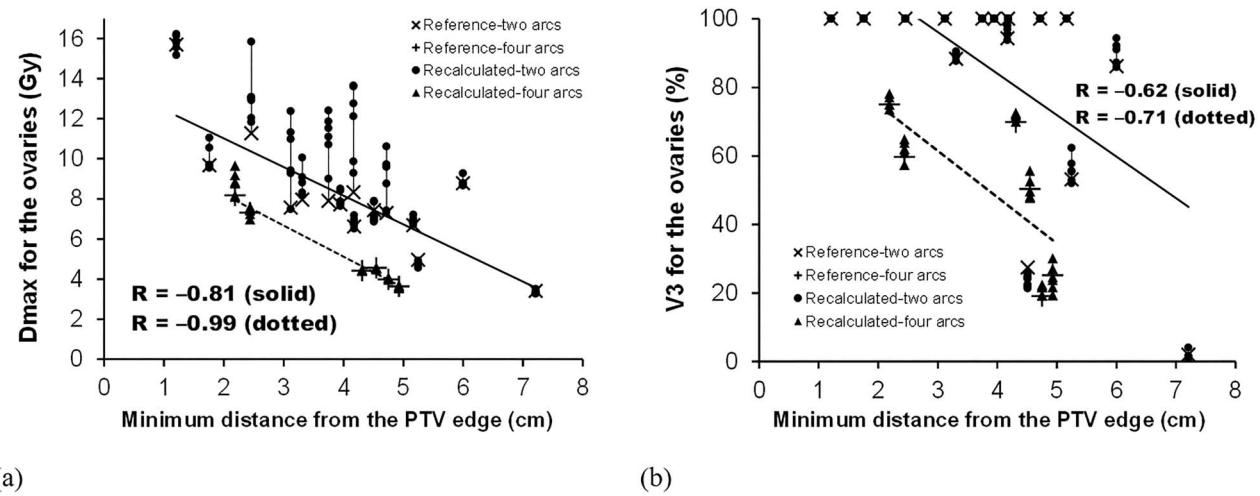


**Fig. 6. Correlations of the minimum distance from the PTV surface with (a) Dmax and (b) V3 for the ovaries. The reference values obtained are indicated by "x" (in two-arc VMAT) or a cross (in four-arc VMAT). The recalculated values are depicted using circles (two-arc VMAT) or triangles (four-arc VMAT). Values for each patient are connected by vertical solid lines. The solid and dashed lines represent the linear regression lines for the reference values of the two-arc and four-arc VMAT, respectively.**

**Table 3. Number of differences in the overall dosimetric parameter for all the 20 patients**

| | | Overall Dosimetric Parameter Difference (count) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | −5% | −3% | −1% | 0% | 1% | 3% | 5% | 7% |
| CTV | D2 | | | 11 | 9 | | | | |
| | D95 | | | 14 | 6 | | | | |
| | D98 | | | 16 | 4 | | | | |
| | CI | | | | 20 | | | | |
| | HI | | | 4 | 16 | | | | |
| Bladder | V45 | | 2 | 2 | 7 | 5 | 3 | 1 | |
| Rectum | V40 | 3 | 6 | 5 | 3 | 2 | 1 | | |
| Small bowel | V40 | 1 | 4 | 6 | 7 | 2 | | | |
| Large bowel | V40 | | | 8 | 11 | | | | |
| Bone marrow | V40 | | | 7 | 13 | | | | |
| | V10 | | | 8 | 12 | | | | |
| Ovary (two-arc) | Dmax | | | 3 | 7 | 3 | 2 | | |
| | V3 | 1 | | 1 | 9 1 | 2 | 1 | | |
| Ovary (four-arc) | Dmax | | | 2 | 4 | | | | |
| | V3 | | | 2 | 1 | 3 | | | |

The overall difference of Dmax for the ovary is shown in Gy.
*Abbreviations:* CTV = clinical target volume; D2, D95 and D98 = minimum doses received in 2%, 95% and 98% of the volume, respectively; CI = Paddick's conformity index; HI = homogeneity index; Dmax = maximum dose; V45, V40, V10 and V3 = volumes receiving 45 Gy, 40 Gy, 10 Gy and 3 Gy, respectively.

In conclusion, only the pitch setup error was moderately correlated with the CTV coverage and strongly correlated with several OARs (i.e. the bladder, the rectum, the small bowel and the bone marrow). Although the CTV is elongated in cervical cancer therapy, rotational setup errors only slightly affected its coverage during postoperative VMAT. However, the pitch setup error occasionally affected the doses received by the bladder or the rectum in the overall fraction. Furthermore, systematic pitch setup errors have a marked impact on the doses received by the bladder or rectum. Thus, rotational setup errors should be corrected by adjusting six-DOF couches to reduce dosimetric differences in OARs.

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## CONFLICT OF INTEREST

First Author (Katsutomo Tsujii) is employed by Varian Medical Systems, Japan.

## PRESENTATION AT A CONFERENCE

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## REFERENCES


1. Zelefsky MJ, Chan H, Hunt M et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 2006;176:1415–19.
2. Marta GN, Silva V, de Andrade Carvalho H et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Onco.* 2014;110:9–15.
3. Heron DE, Gerszten K, Selvaraj RN et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms. *Gynecol Oncol* 2003;91:39–45.
4. Amro H, Hamstra DA, McShan DL et al. The dosimetric impact of prostate rotations during electromagnetically guided external-beam radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:230–6.
5. Jiang P, Zhang X, WS. et. al. Set-up error and dosimetric analysis of HexaPOD evo RT 6D couch combined with cone beam CT image-guided intensity-modulated radiotherapy for primary malignant tumor of the cervical spine. *J Appl Clin Med Phys* 2020;21:22–30.
6. Guckenberger M, Meyer J, Vordermark D et al. Magnitude and clinical relevance of translational and rotational patient setup errors: a cone-beam CT study. *Int J Radiat Oncol Biol Phys* 2006;65:934–42.
7. Weiss E, Vorwerk H, Richter S et al. Interfractional and intrafractional accuracy during radiotherapy of gynecologic carcinomas: a comprehensive evaluation using the ExacTrac system. *Int J Radiat Oncol Biol Phys* 2003;56:69–79.
8. Laursen LV, Elstrom UV, Vestergaard A et al. Residual rotational set-up errors after daily cone-beam CT image guided radiotherapy of locally advanced cervical cancer. *Radiother Oncol* 2012;105:220–5.
9. Stromberger C, Gruen A, Wlodarczyk W et al. Optimizing image guidance frequency and implications on margins for gynecologic malignancies. *Radiat Oncol* 2013;8:110. https://pubmed.ncbi.nlm.nih.gov/23638800/
10. Laaksomaa M, Kapanen M, Tulijoki T et al. Evaluation of overall setup accuracy and adequate setup margins in pelvic image-guided radiotherapy: comparison of the male and female patients. *Med Dosim* 2014;39:74–8.
11. Yao L, Zhu L, Wang J et al. Positioning accuracy during VMAT of gynecologic malignancies and the resulting dosimetric impact by a 6-degree-of-freedom couch in combination with daily kilovoltage cone beam computed tomography. *Radiat Oncol* 2015;10:104.
12. Zhang X, Shan GP, Liu JP et al. Margin evaluation of translational and rotational set-up errors in intensity modulated radiotherapy for cervical cancer. *Springerplus* 2016;24:153.
13. Toita T, Ohno T, Kaneyasu Y et al. A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. *Jpn J Clin Oncol.* 2010;40:456–63.
14. Ueda Y, Ohira S, Isono M et al. Strategies for reducing ovarian dose in volumetric modulated arc therapy (VMAT) for postoperative uterine cervical cancer. *Br J Radiol* 2018;91: 1081:20160777.
15. NRG Oncology RTOG1203. A randomized phase III study of standard vs. IMRT pelvic radiation for post-operative treatment of endometrial and cervical cancer (TIME-C). *RTOG* 2015;1203.https://www.nrgoncology.org/Clinical-Trials/Protocol/rtog-1203?filter=rtog-1203 (19 May 2021, data last accessed)
16. Chambers S, Chambers J, Kier R et al. Sequelae of lateral ovarian transposition in irradiated cervical cancer patients. *Int J Radiat Oncol Biol Phys* 1991;20:1305–8.
17. Wallace WH, Thomson AB, Saran F et al. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005;62:738–44.
18. Paddick I. A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. *J Neurosurg.* 2000;93:219–22.
19. International Commission on Radiation Units and Measurements. Report 83: Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). *J ICRU* 2010;10:1–106.
20. Remeijer P, Geerlof E, Ploeger L et al. 3-D portal image analysis in clinical practice: an evaluation of 2-D and 3-D analysis techniques as applied to 30 prostate cancer patients. *Int J Radiat Oncol Biol Phys* 2000;46:1281–90.
21. Kaiser A, Schultheiss TE, Wong JY et al. Pitch, roll, and yaw variations in patient positioning. *Int J Radiat Oncol Biol Phys.* 2006;66:949–55.
22. Ahmad R, Hoogeman MS, Quint S et al. Residual setup errors caused by rotation and non-rigid motion in prone-treated cervical cancer patients after online CBCT image-guidance. *Radiotherapy and Oncology* 2012;103:322–6.
23. Ahmad R, Hoogeman MS, Quint S et al. Inter-fraction bladder filling variations and time trends for cervical cancer patients assessed with a portable 3-dimensional ultrasound bladder scanner. *Radiotherapy and Oncology* 2008;89:172–9.
24. Fu W, Yang Y, Yue NJ et al. Dosimetric influences of rotational setup errors on head and neck carcinoma intensity-modulated radiation therapy treatments. *Med Dosim* 2013;38:125–32.
25. Murphy MJ. Image-guided patient positioning: if one cannot correct for rotational offsets in external-beam radiotherapy setup, how should rotational offsets be managed? *Med Phys* 2007;34: 1880–3.
26. Hwang JH, Yoo HJ, Park SH et al. Association between the location of transposed ovary and ovarian function in patients with uterine cervical cancer treated with (postoperative or primary) pelvic radiotherapy. *Fertil Steril* 2012;97:1387–93 e1381–2.

27. Yoon A, Lee YY, Park W et al. Correlation between location of transposed ovary and function in cervical cancer patients who underwent radical hysterectomy. *Int J Gynecol Cancer* 2015;25:688–93.
28. Husseinzadeh N, van Aken M, Aron B. Ovarian transposition in young patients with invasive cervical cancer receiving radiation therapy. *Int J Gynecol Cancer.* 1994;4:61–5.
29. Van Eijkeren MA, Van Der Wijk I, El Sharouni SY et al. Benefits and side effects of lateral ovarian transposition (LOT) performed during radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer. *Int J Gynecol Cancer.* 1999;9: 396–400.
30. Kase KR, Svensson GK, Wolbarst AB et al. Measurements of dose from secondary radiation outside a treatment field. *Int J Radiat Oncol Biol Phys* 1983;9:1177–83.
31. Qiu Y, Moiseenko V, Aquino-Parsons C et al. Equivalent doses for gynecological patients undergoing IMRT or RapidArc with kilovoltage cone beam CT. *Radiother Oncol* 2012;104:257–62.
32. International Commission on Radiation Units and Measurements. *Report 62. Prescribing, Recording, and Reporting Photon Beam Therapy (supplement to ICRU Report 50)*. Bethesda, MD, 1999.
33. Wang X, Yu M, Wang J et al. An assessment of interfractional bladder, rectum and vagina motion in postoperative cervical cancer based on daily cone-beam computed tomography. *Mol Clin Oncol* 2016;4:271–7.
34. Jhingran A, Salehpour M, Sam M et al. Vaginal motion and bladder and rectal volumes during pelvic intensity-modulated radiation therapy after hysterectomy. *Int J Radiat Oncol Biol Phys* 2012;82:256–62.
35. Jurgenliemk-Schulz IM, Toet-Bosma MZ, de Kort GA et al. Internal motion of the vagina after hysterectomy for gynaecological cancer. *Radiother Oncol* 2011;98:244–8.
36. Ma DJ, Michaletz-Lorenz M, Goddu SM et al. Magnitude of interfractional vaginal cuff movement: implications for external irradiation. *Int J Radiat Oncol Biol Phys* 2012;82:1439–44.
37. Rash D, Hagar Y, Cui J et al. Interfraction motion of the vaginal apex during postoperative intensity modulated radiation therapy: are we missing the target? *Int J Gynecol Cancer* 2013;23: 385–92.
38. Harris EE, Latifi K, Rusthoven C et al. Assessment of organ motion in postoperative endometrial and cervical cancer patients treated with intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2011;81:e645–50.