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Scientific Article

Optimal Correction Strategy of Image Guided Radiation Therapy Including the Paraortic Lymph Node Region in Patients With Cervical Cancers

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Purpose: The clinically accepted planning target volume margin for radiation therapy to the paraortic nodal region in cervical cancer patients is 5 mm. However, the comprehensive alignment and variability from the pelvic bone to all lumbar vertebrae are undetermined. This study aims to quantify the residual setup errors between the pelvic bone and lumbar vertebrae and determine the optimal correction strategy for patients with cervical cancer.

Materials and Methods: Fifteen patients underwent pretreatment mega-voltage computed tomography scans (375 total fractions). Residual setup errors and required margins for each lumbar vertebra were calculated based on registrations accounting for pelvic rotation and translation.

Results: The systematic residual errors (1 SD) at L1, L2, L3, L4, and L5 using pelvic bone registration were 6.5, 4.9, 3.1, 1.5, and 0.6 mm in the anterior-posterior (AP) direction, 3.1, 2.3, 1.4, 0.6, and 0.3 mm in the right-left direction, and 2.7, 2.2, 1.7, 1.0, and 0.5 mm in the superior-inferior direction, respectively. The residual setup errors were the largest in the AP direction. Registration based on the pelvic bone required margins in the AP direction of 16.0, 12.1, 7.7, 3.6, and 1.3 mm for L1, L2, L3, L4, and L5, respectively, whereas registration based on L3 required margins of 8.8, 4.8, 4.4, 7.1, and 7.7 mm for L1, L2, L4, L5, and pelvic bone, respectively.

Conclusions: Considerable local setup variability was found in patients with cervical cancer. After reviewing the corrective strategies, we determined that L3-based registration effectively minimized the required margins.

Introduction

Standard treatment for locally advanced cervical cancer is external-beam radiation therapy, concomitant chemotherapy, and brachytherapy. External-beam radiation therapy has been used in 3-dimensional conformal radiation therapy and intensity-modulated radiation therapy (IMRT). IMRT facilitates prescriptive coverage of the target while sparing surrounding critical organs at risk (OAR). Furthermore, IMRT for cervical cancers reduces gastrointestinal and hematologic toxicity.[1-3] Cervical cancers in patients who have metastatic disease of the paraortic lymph node (PAN) at diagnosis or who are at a high risk of recurrence can be effectively controlled by irradiation to the PAN.[4,5]

Patients with cervical cancer in whom the PAN is included within the clinical target volume receive an

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irradiation field of approximately 40 cm in the superior-inferior direction. Accuracy of the patient's daily setup for radiation therapy is essential because IMRT provides a highly conformal dose distribution that results in a steep dose fall-off to normal tissue.[6] Among the rotational setup errors in patients with cervical cancer, pitch direction error reportedly affects the dose to the target and OAR.[7-9]

The margin from clinical target volume to planning target volume (PTV) for the PAN was recommended to be 5 mm in the EMBRACE II protocol, a trial for cervical cancer, a reduction from the more conventional 10 mm.[10] The trial aims to reduce margins and, consequently, minimize intestinal morbidity, under the assumption that daily setup errors are rectified through daily imaging. The EMBRACE Ⅱ protocol cited results by Laursen et al[7] as evidence for the margin reduction. They found that setup errors could be efficiently improved by performing 6-dimensional (6D) registration around the pelvic regions. However, the report was limited to the evaluation of setup errors near the pelvic region due to the 16 cm (craniocaudal direction) imaging range of a cone beam computed tomography. Such evaluation can therefore only be performed up to the lumbar vertebrae 4 and 5 (L4 and L5) levels. Pelvic bone and vertebrae interact with each other through sacral and iliac rotation, that is, nutation and counternutation.[11] The PAN follows the motion of the vertebrae; hence, it is affected by their bending. Registration based on the pelvic bone may therefore cause residual setup errors, specifically in the upper lumbar vertebra. To the best of our knowledge, no studies have properly evaluated the residual setup error of the PAN. Our institution uses helical tomotherapy, and the mega-voltage computed tomography (CT) (MVCT) enables us to scan up to 135 cm; hence, we can analyze setup errors including the PAN.

The aim of this study was to quantify the residual setup errors between the pelvic bone and lumber vertebrae and determine the optimal correction strategy of IMRT including the PAN region in patients with cervical cancer.

Materials and Methods

Patient selection

Retrospectively enrolled in the study were 15 patients with locally advanced cervical cancer, including the PANs as a target. Federation of Gynecology and Obstetrics (2018) stage distribution was as follows: stage IIIC2 = 12, stage IVA = 1, and stage IVB = 2. All patients received a total of 25 fractions of radiation therapy using TomoTherapy HD (Accuray, Madison, WI) at our hospital from April 2018 to November 2022. This retrospective study was approved by our institutional ethics committee (Approval No. 3826), and treatment was performed in accordance with the tenets of the Declaration of Helsinki.

Clinical setup and imaging protocol

Each patient underwent kilo-voltage CT (kVCT) scans (Acquilion LB, Canon Medical Systems, Otawara, Japan) with a 2-mm slice thickness for radiation therapy planning. Patients were scanned feet-first using Vac-Lok (Civco, Orange City, IA) for immobilization of the lower extremities, with the upper extremities elevated using wing boards (Civco). The patient's body surface and Vac-Lok were marked for alignment with the treatment room laser. The kVCT image resolution was 512 × 512 pixels. CT images were transferred to the Eclipse system (Varian Medical Systems, Palo Alto, CA), solely for contouring purposes. After all structures (the target and OARs) were contoured, the CT images and structure set were sent to the Planning Station (Accuray). Before each treatment, patients were set up in the same position for CT scanning to align the treatment room laser with the skin surface and Vac-Lok markings. The patient then underwent an MVCT scan before every treatment fraction with the Helical TomoTherapy. When the target was out of PTV in the MVCT image, a re-setup was performed. In such cases, only the post-re-setup MVCT image was applied to this study. All MVCT images of each patient (375 fractions in total) were analyzed.

Residual setup errors

The pretreatment MVCT images were transferred to the Eclipse system for reregistration analysis with kVCT images. Reregistration was performed using the kVCT image as the source image and the MVCT image as the target image. Retrospective reregistration of kVCTs and MVCTs was performed using image registration (downhill simplex method and mutual information) with the Eclipse system. Reregistration was conducted for regions of interest determined at 6 bone landmarks (L1, L2, L3, L4, L5 vertebrae, and the pelvic bone), as shown in Fig. 1. The image reregistration was performed using a bone window, and the region of interest encompassed a part of the pelvic region included in the MVCT field of view, excluding the surface skin but including all pelvic bone structures.[7]

The initial step of reregistration involved 6D reregistration, allowing rotation and translation for the pelvic bone and recording the correction values. Subsequently, reregistration was conducted with only translational directions allowed for each vertebra while retaining the rotation of the pelvic bone. Residual setup error was defined as the difference between the translational variation of the pelvic bone and the lumbar vertebrae. Translational variations were defined as anterior-posterior (δAP),

Figure 1 Regions of interest for each lumbar vertebra and pelvic bone mapped on registration landmarks.

right-left (δRL), and superior-inferior (δSI), whereas pelvic bone rotational variations were defined as pitch (rotation around the transverse axis), yaw (rotation around the sagittal axis), and roll (rotation around the longitudinal axis). When the correction values of δAP, δRL, and δSI are positive, the MVCT image moves to the anterior, right, and foot sides, respectively, whereas positive correction values for pitch, yaw, and roll result in the MVCT image moving backward, rightward, and rightward, respectively, all with respect to kVCT.

To assess whether vertebral translational variation is associated with pelvic rotation, the correlation coefficients were quantified by the Pearson product-moment correlation coefficient.

Correction strategy

We examined margins and margin-minimizing registration landmarks as a correction strategy. A first-order approximation to the formula proposed by Van Herk et al[12,13] for a rigid-body setup was used to evaluate the local anisotropic margins required for 6 bone landmarks with respect to pelvic bending:

$$m = 2.5\Sigma + 0.7\sigma, \quad (1)$$

where Σ is the systematic setup error, and σ is the random setup error.

Results

Residual setup errors

The mean and SD of pelvic bone rotation obtained by retrospective 6D reregistration for pitch, yaw, and roll were 0.5 ± 2.1° (range: −6.0 to 6.3°), −0.1 ± 1.0° (range: −3.1 to 1.9°), and 0.0 ± 1.5° (range: −3.5 to 3.5°), respectively. The Σ values of pelvic bone rotation obtained by retrospective 6D reregistration for pitch, yaw, and roll are 2.1°, 1.4°, and 1.0°, and for σ are 0.6°, 1.5°, and 1.0°, respectively. The residual setup error was assessed by translational variation of the vertebra with respect to the pelvic bone's 6D reregistration. Residual setup errors of each vertebra are shown in Table 1. There were no variations >5 mm in any direction in L4 and L5, but there were variations >5 mm in L1, L2, and L3 for δAP, δRL, and δSI. Translational variations in δAP > 5 mm were observed in 45%, 30%, and 12% of all fractions for L1, L2, and L3, respectively. Similarly, δRL and δSI > 5 mm were observed in 13%, 5%, and 1%, respectively, and 9%, 3%, and 1% for L1, L2, and L3, respectively. The correlation coefficients between pelvic bone rotation and lumbar vertebral translation variation are shown in Table 2. Only pelvic bone pitch rotation and δAP showed a strong correlation in the L1, L2, and L3 levels. Scatter plots of δAP with respect to pelvic bone pitch are shown in Fig. 2.

Correction strategy

The local anisotropic margins (Eq. 1) required for registration by the 6 bone landmarks are summarized in Table 3. In the case of registration based on the pelvic bone, a margin of 5 mm was sufficient for L4 and L5. However, for L1, L2, and L3, a margin of 5 mm was insufficient, especially in the AP direction.

Discussion

In this study, we assessed the residual setup errors from L1 to the pelvic bone in patients with cervical cancer using pretreatment MVCT images. Our findings align with those of Laursen et al,[7] demonstrating that the clinically applied PAN margin of 5 mm effectively covers the L5 and L4 levels when registration is based on the pelvic bone. However, in the L1, L2, and L3, a 5-mm PTV margin may be insufficient, and a larger PTV margin would be required, particularly in the AP direction (Table 3). Previous studies have shown that pelvic bone rotational variations are greater in terms of pitch than yaw or roll.[7-9,14] Our results support these previously published findings. This result is consistent with the difficulty encountered in correcting pelvic bone pitch rotation using skin markers. Our study showed a strong correlation between the pelvic bone pitch rotation and the AP translational variation of the vertebrae. Essentially, the AP displacement of the lumbar vertebrae was shown to be due to the pitch rotation of the pelvic bone. The scatter plot in Fig. 2 shows that when the pelvis on a pretreatment MVCT is tilted backward to register against the kVCT, the L1 on the pretreatment MVCT tilts backward even further, leading to a larger setup error. This phenomenon is associated with the curvature of the pelvis and lumbar vertebrae (nutation and counternutation[11]). Even if strict registration based on pelvic bone is performed with these variations, it is difficult to align with all the landmarks. It was suggested that the existing margin recipe may be insufficient on the head side, compared with the range evaluated by Laursen et al.[4] In the EMBRACE I protocol, a 10-mm margin is set for the elective lymph node target. This wide-margin recipe is necessary to compensate for the uncertainty of not being able to implement daily image guidance. However, wide margins can result in high doses being applied to the surrounding OARs. Therefore, a margin recipe of no more than 10 mm should be clinically applied when daily image guidance is available.[10] L3-based registration minimized the required margins to less than 10 mm for all of the areas.

6D registration based on the pelvic bone is insufficient to correct for variations due to pelvic and lumbar vertebra curvature. Consideration of corrective strategies to compensate for setup is therefore necessary. First, for example, there may be a need for a device to correct a patient's twist, as devised by Shimizu et al[15] for the head and neck region. However, its clinical application is still difficult because interference with immobilization devices such as Vac-Loks must be considered. Next, the margin size to reduce the dose to normal tissue while compensating for target coverage should then be considered. Based on our results, a margin of 16 mm in the AP direction is required at the L1 level when registration is based on the pelvic region. Nevertheless, an unnecessary increase in the margin would result in the OAR being included in the PTV and the benefits of IMRT would be lost.

We calculated the best single couch correction based on the variations of all bone landmarks, similar to van Kranen et al[13] who investigated the optimal correction strategy in the head and neck region. Our results suggest that L3-based registration could minimize the variability of the overall setup. Furthermore, the incorporation of anisotropic margins is an effective way to deal with complex setup variations.[16]

The limitation of this study is the substitution of bone structures for positioning lymph nodes and the uterus. The PANs are associated with the lumbar vertebrae,[17] whereas the uterine position may vary depending on bladder and rectal contents.[18-20] Conversely, registration using bone structures is commonly used in image guided radiation therapy in patients with cervical cancers.[7,8] The goal of our study was to establish a correction strategy for patients with cervical cancers; hence, we employed registration using bone structures. In addition, another issue arises from the setup errors in cervical cancer patients, which are complex and influenced by nutation and counternutation. When dealing with setup errors, it is conceivable that the variability would increase with increasing

Table 1 **Residual setup errors of the vertebrae after correction using the 6D reregistration based on the pelvic bone**

	δAP (mm)		δRL (mm)		δSI (mm)	
Vertebrae	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
L1	0.0 ± 6.5	−18.6 to 18.0	1.4 ± 3.1	−5.9 to 15.1	0.0 ± 2.7	−10.2 to 8.1
L2	−0.3 ± 4.9	−12.9 to 13.7	1.0 ± 2.3	−4.2 to 10.6	0.3 ± 2.2	−8.1 to 7.2
L3	−0.3 ± 3.1	−8.3 to 9.1	0.7 ± 1.4	−3.5 to 6.1	0.3 ± 1.7	−8.0 to 4.6
L4	−0.2 ± 1.5	−4.5 to 4.8	0.3 ± 0.6	−1.8 to 2.8	0.1 ± 1.0	−3.9 to 2.7
L5	−0.2 ± 0.6	−2.1 to 1.8	0.1 ± 0.3	−3.1 to 1.9	0.1 ± 0.5	−2.6 to 1.7

Abbreviations: δAP = anterior-posterior; δRL = right-left; δSI = superior-inferior.

Table 2 **Pearson's product-moment correlation coefficient between the rotation of the pelvic bone and the translational variation of the lumbar vertebrae**

	L1			L2			L3			L4			L5		
Pelvic rotation	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**
Pitch	0.89	0.05	−0.57	0.86	0.02	−0.54	0.80	0.01	−0.41	0.63	−0.01	−0.35	0.14	0.00	0.03
Yaw	0.10	−0.52	−0.04	0.10	−0.51	−0.05	0.06	−0.45	−0.01	0.05	−0.29	−0.13	0.07	0.13	0.03
Roll	0.15	0.46	−0.11	0.14	0.42	−0.11	0.14	0.33	−0.10	0.14	0.19	−0.11	0.08	−0.18	−0.06

Abbreviations: AP = anterior-posterior; RL = right-left; SI = superior-inferior.

Table 3 **Local anisotropic margins calculated by formula (1) using 6 bone registration landmarks**

	L1			L2			L3			L4			L5			PB		
Target structure	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**	**AP**	**RL**	**SI**
L1	-	-	-	4.3	2.5	2.2	8.8	4.8	3.6	13.0	6.8	5.1	15.5	7.8	6.3	16.0	7.8	6.9
L2	4.3	2.5	2.2	-	-	-	4.8	2.5	1.9	9.0	4.5	3.6	11.6	5.6	4.9	12.1	5.6	5.5
L3	8.8	4.8	3.6	4.8	2.5	1.9	-	-	-	4.4	2.2	2.3	7.1	3.2	3.5	7.7	3.3	4.3
L4	13.0	6.8	5.1	9.0	4.5	3.6	4.4	2.2	2.3	-	-	-	2.8	1.3	1.9	3.6	1.4	2.5
L5	15.5	7.8	6.3	11.6	5.6	4.9	7.1	3.2	3.5	2.8	1.3	1.9	-	-	-	1.3	0.5	1.1
PB	16.0	7.8	6.9	12.1	5.6	5.5	7.7	3.3	4.3	3.6	1.4	2.5	1.3	0.5	1.1	-	-	-

Abbreviation: AP = anterior-posterior; PB = pelvic bone; RL = right-left; SI = superior-inferior.

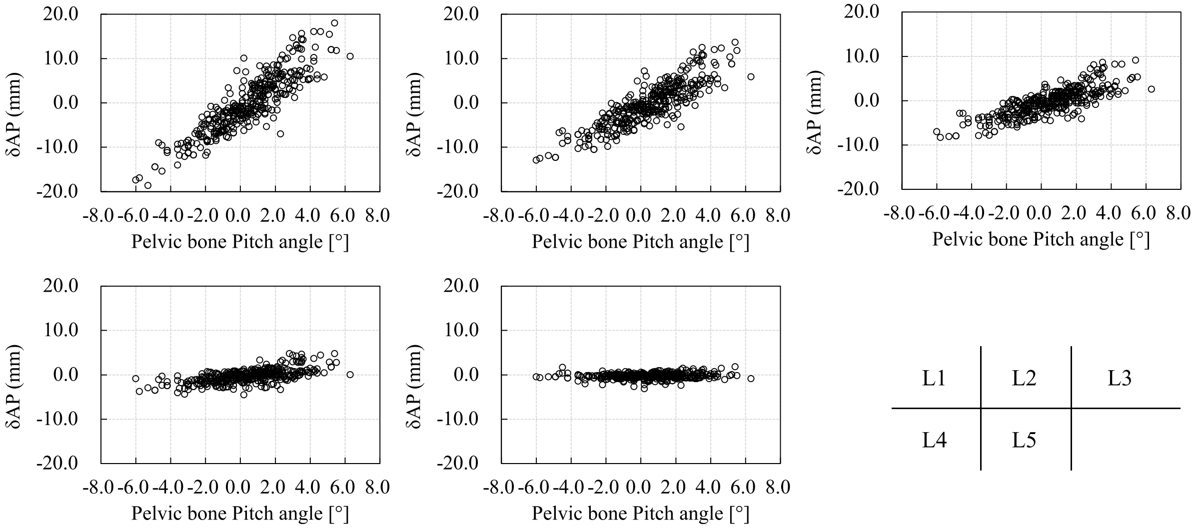

Figure 2 Relationship between the angle of pelvic bone pitch and vertebral δAP.
Abbreviation: δAP = anterior-posterior.

distance from the correction point, despite optimal couch correction. In our study, the L3-based correction strategy required a margin exceeding 5 mm for L1, L5, and pelvic bone. Therefore, we need to develop an assistive device, such as lumbar support, to limit the setup errors caused by pitch rotation of the pelvic bones.

Conclusion

The registration based on the pelvic bone caused setup errors >5 mm at L1, L2, and L3 levels in image guided radiation therapy including the PAN region for patients with cervical cancers. L3-based registration effectively minimized the required margins to less than 10 mm.

Disclosures

None.

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