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Analysis of local setup errors of sub-regions in cone-beam CT-guided post-mastectomy radiation therapy

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ABSTRACT

The purpose of the study was to quantify local setup errors and evaluate the planning target volume (PTV) margins for sub-regions in cone-beam computed tomography (CBCT)-guided post-mastectomy radiation therapy (PMRT). The local setup errors of 20 patients undergoing CBCT-guided PMRT were analysed retrospectively. Image registration between CBCT and planning CT was performed using four sub-regions of interest (ROIs): the supraclavicular area (S_{ROI}), ipsilateral chest wall region (C_{ROI}), ipsilateral chest wall plus supraclavicular region ($S_{ROI} + C_{ROI}$) and vertebral region (T_{ROI}). Bland–Altman analysis, correlation, local setup errors and PTV margins among these ROIs were evaluated. There was no significant consistency or correlation for registration results between the T_{ROI} and the C_{ROI} or S_{ROI} regions on any translational axis. When using the $S_{ROI} + C_{ROI}$ as the ROI, the systematic error (Σ) and random error (σ) of the local setup errors for the C_{ROI} region were 1.81, 1.19 and 1.76 mm and 1.84, 2.64 and 3.00 mm along the medial–lateral (ML), superior–inferior (SI) and anterior–posterior (AP) directions, respectively. The PTV margins for the C_{ROI} region were 5.80, 4.82 and 6.50 mm. The Σ and σ of the local setup errors for the S_{ROI} region were 1.29, 1.15 and 0.77 mm and 1.96, 2.65 and 2.2 mm, respectively, and the PTV margins were 4.59, 4.73 and 3.47 mm. Large setup errors and local setup errors occur in PMRT. The vertebral body should not be a position surrogate for the supraclavicular region or chest wall. To compensate for the local setup errors, different PTV margins are required, even with CBCT guidance.

Keywords: local setup errors; CBCT guidance; post-mastectomy radiation therapy

INTRODUCTION

Post-mastectomy radiation therapy (PMRT) is the main treatment for breast cancer patients. With precise radiotherapy, the local control rate and the overall survival rate of patients can be improved [1–3]. Radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy can increase the dose of the target area while protecting the surrounding normal tissues [4]. To verify the accuracy of positioning, electronic portal images (EPIs), cone beam computed tomography (CBCT) and optical surface imaging are commonly used. In total breast radiotherapy, Michalski *et al.* [5] reported setup errors ranging from 2.6 to 22.9 mm by EPIs. Batumalai *et al.* [6] reviewed different studies that depended on different registration methods and found that the ranges of the systematic errors were 1.2–5.7, 1.3–3.8 and 0.5–5.7 mm, and the random errors were 1.0–7.3, 1.2–4.1 and 0.9–4.0 mm in the medial–lateral (ML), superior–inferior (SI) and anterior–posterior (AP) direction, respectively. Sonmez *et al.* [7] concluded that setup errors in breast cancer radiotherapy should be strictly controlled below 5 mm. These data show that there are large differences in setup errors in breast cancer radiotherapy.

The treatment area for PMRT also includes the chest wall and supraclavicular, axillary and internal mammary lymphoid areas, and the related organs at risk are the cervical vertebrae, lungs, heart, and so

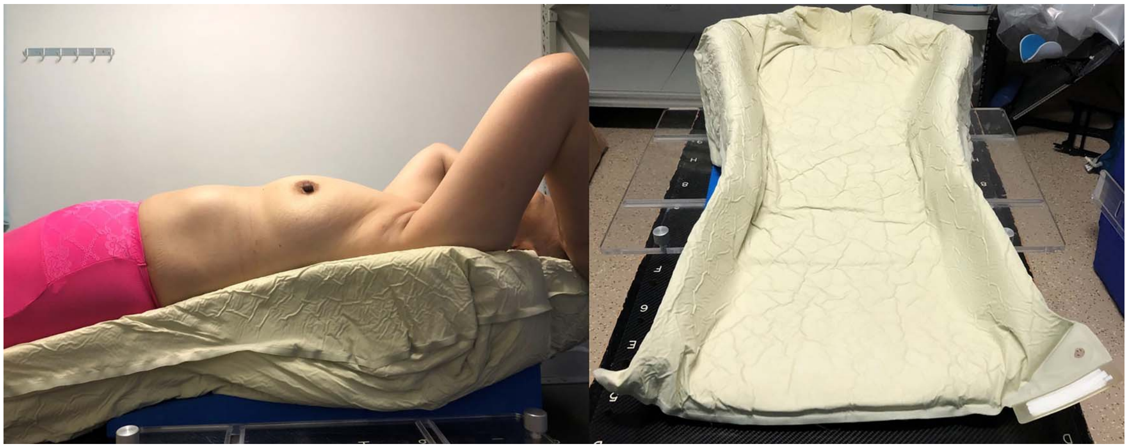

Fig. 1. The patient was immobilized with a CIVCO Breast Board Cushion (vacuum bag, size 90 × 55 cm, volume 15 L).

forth. The relative positions among these regions may vary, resulting in local deformation errors for each region. In clinical practice, the supraclavicular region plus the chest wall ($S_{ROI} + C_{ROI}$) are deemed as a single region of interest (ROI) for registration in CBCT-guided radiotherapy. The registration results would be averaged for these two sub-regions (S_{ROI} and C_{ROI} region) using $S_{ROI} + C_{ROI}$ as an ROI, resulting in an underestimation of local setup errors and dose uncertainty in the region of the supraclavicular area (S_{ROI}) or chest wall (C_{ROI}). Meanwhile, the thoracic vertebrae (T_{ROI}) are far from the $S_{ROI} + C_{ROI}$ region, and the difference between T_{ROI} and other ROIs should be evaluated. Therefore, to ensure position accuracy and set the appropriate clinic target volume to planning target volume (CTV–PTV) margin, the local setup errors should be quantified for these sub-regions using different ROIs in CBCT-guided radiotherapy for PMRT.

MATERIALS AND METHODS

Patients

Twenty post-mastectomy breast cancer patients receiving radiotherapy from March 2015 to March 2017 in our department were randomly enrolled. Written consent was obtained from all patients prior to treatment in the study. For 10 patients the left supraclavicular region and chest wall were treated. For the other 10 patients the right supraclavicular region and chest wall were treated. The median age of the patients was 46 years (range, 34–61 years).

Immobilization

The CIVCO Breast Board Cushion (vacuum bag, size 90 × 55 cm, volume 15 L; CIVCO Radiotherapy, Orange City, IA, USA) was laid on a 15-degree wedge plate, and the upper boundary of the cushion was formed to fit the shape of the patient's head and to limit the longitudinal movement of the head. The abduction of the upper limb on the involved side was greater than 90°. The vacuum pads on both sides of the arm ensured that the arms were secured as much as possible to prevent them from moving and pulling the skin of the adjacent chest, which would result in deformation of the skin mark (Fig. 1).

Simulation and planning

Free-breathing patients were simulated using Philips Gemini 64-slice CT with a 3-mm slice thickness from the chin to the lower edge of the liver with intravascular contrast. According to the *RTOG Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions*[8], the target (chest wall, supraclavicular lymph nodes) and organs at risk (i.e., heart, ipsilateral lung, contralateral breast and the spinal cord) were delineated. The treatment plan was generated using the RayStation 4.7 (RaySearch, Stockholm, Sweden) treatment-planning system.

CBCT scan

The CBCT images were obtained by XVI 4.5 (Synergy, Elekta, Crawley, UK). The number of frames per CBCT acquisition was ~400. The scanning parameters were tube voltage 100 kV, tube current 36.1 mA, S20 F1 filter plate, acquisition speed 5.5 frames/s and acquisition angle 50–210°.

Local setup analysis

The local setup errors were analysed offline using four sub-ROIs (see Fig. 2 for details). These four sub-regions included (i) the supraclavicular region (S_{ROI}), from the cricoid to the lower edge of the collarbone head in the longitudinal direction and from the cervical vertebra to the humeral head in the lateral direction; (ii) the ipsilateral chest wall region (C_{ROI}), from the humeral head to the lower edge of the PTV in the longitudinal direction and from the midline of the body to the outer 1 cm of the chest wall in the lateral direction; (iii) the ipsilateral chest wall plus supraclavicular region ($S_{ROI} + C_{ROI}$), the combination of S_{ROI} and the C_{ROI} region; and (iv) the vertebral region (T_{ROI}), from ~C5–T8 in the longitudinal direction, from the anterior of the vertebral body to the posterior boundary of the spinous in the vertical direction. The image registration protocols of our institution are as follows. The automatic registration "gray value (T + R)" (3 translational directions and 3 rotations directions) was used to obtain the coarse registration first, and then manual fine adjusting followed. Regarding S_{ROI}, we focused on the registration of the clavicle and cervical vertebrae. We mainly considered rib registration for C_{ROI}. Automatic registration was mainly used for $S_{ROI} + C_{ROI}$, unless there was a significant registration error. The registration of thoracic vertebrae was used for T_{ROI}. The systematic errors (Σ) and random errors (σ) were computed along the ML, SI and AP axes, and the rotation errors along the pitch, roll and yaw axes were also recorded. To quantify local setup errors, the region $S_{ROI} + C_{ROI}$ was set as the reference ROI. The differences in registration results between $S_{ROI} + C_{ROI}$ and S_{ROI} or C_{ROI} appeared to be local setup errors. Meanwhile, the differences in registration results between T_{ROI} and other ROIs were evaluated.

Statistical analysis

One-way analysis of variance with Games-Howell *post hoc* tests was used to compare the setup errors among the four sub-regions (S_{ROI}, C_{ROI}, $S_{ROI} + C_{ROI}$, and T_{ROI}). Pearson's correlation coefficient was used to analyse the correlation of the local setup errors in the four sub-regions. SPSS 19.0 was used to perform the above analysis. Bland–Altman analysis (using Python 3.7.4) was used to assess the ranges of agreement between the registration results of these ROIs.

CTV–PTV margin

According to ICRU Report 50 and Report 62 [9, 10], to reduce placement error and the impact of patient and organ movement on the target area, a ring should be placed outside the CTV. To ensure the CTVs obtain at least 95% of the prescribed dose for 90% of patients, this study used the following simplified margin calculation by Van Herk *et al.* [11]: $2.5\ \Sigma + 0.7$, where Σ is the standard deviation (SD) of the individual means for each ROI registration result per patient, and σ is the root mean square of the individual SD for each ROI registration result per patient.

RESULTS

Table 1 shows that in the AP direction, the difference in registration results between the S_{ROI} and C_{ROI}, C_{ROI} and T_{ROI}, $S_{ROI} + C_{ROI}$, and T_{ROI} regions was statistically significant. In the roll direction, the difference in registration results between the S_{ROI} and T_{ROI} regions was statistically significant. In the yaw direction, the difference between the S_{ROI} and C_{ROI}, S_{ROI} and $S_{ROI} + C_{ROI}$, S_{ROI} and T_{ROI}, and C_{ROI} and $S_{ROI} + C_{ROI}$ registration results was statistically significant.

The correlation analysis of the registration results among different ROIs showed that the S_{ROI}, C_{ROI}, and $S_{ROI} + C_{ROI}$ regions had a very strong correlation in all translational directions. There was a strong correlation between the registration results of $S_{ROI} + C_{ROI}$ and C_{ROI} in the pitch direction, $S_{ROI} + C_{ROI}$ and S_{ROI} in the roll direction, and $S_{ROI} + C_{ROI}$ and S_{ROI} in the yaw direction. There was no significant correlation between the registration results of T_{ROI} and any other ROIs (maximum correlation coefficient $r = -0.30$, $P < 0.01$). See Table 2 for details.

The registration results of ROIs, the difference among these ROIs, and the corresponding PTV margins are shown in Table 3. The difference in registration results between T_{ROI} and other ROIs was considerable. The systematic and random errors ranged from 4.19 to 8.90 mm, and the corresponding PTV margins ranged from 14.59 to 22.13 mm. The local setup errors of the S_{ROI} (the difference in registration results between $S_{ROI} + C_{ROI}$ and S_{ROI}) and C_{ROI} (the difference in registration results between $S_{ROI} + C_{ROI}$ and C_{ROI}) were smaller than the registration results between T_{ROI} and other ROIs. The Σ and σ of the local setup error for C_{ROI} were 1.81, 1.19 and 1.76 mm and 1.84, 2.64 and 3.00 mm, respectively, and the corresponding PTV margins were 5.80, 4.82 and 6.50 mm. The Σ and σ of the local setup error for S_{ROI} were 1.29, 1.15 and 0.77 mm and 1.96, 2.65 and 2.2 mm, respectively, and the corresponding PTV margins were 4.59, 4.73 and 3.47 mm.

The Bland–Altman analysis revealed good agreement in registration results between C_{ROI} and $S_{ROI} + C_{ROI}$ and between S_{ROI} and $S_{ROI} + C_{ROI}$. However, there was no significant consistency in registration results between the T_{ROI} region and the C_{ROI} or S_{ROI} region on any translational axis. Figure 3 shows the Bland–Altman analysis between C_{ROI} and $S_{ROI} + C_{ROI}$ and between S_{ROI} and $S_{ROI} + C_{ROI}$ in the translational directions.

DISCUSSION

Setup errors in breast cancer radiotherapy are larger than the rigid structures, and the present study found that the setup errors of the $S_{ROI} + C_{ROI}$ region ranged from 3.21 to 4.67 mm. The corresponding CTV–PTV margin was >10 mm, similar to the study by Popja *et al.* [4]. Strydhorst *et al.* found systematic and random errors in the ML, SI and AP directions of the chest wall of 2.7, 9.8 and 4.1 mm and 4.0, 12.0 and 4.5 mm [12]. Koseoglu *et al.* reported that the setup errors ranged from 4 to 13 mm [13]. Meanwhile, Zhang *et al.* found that the ipsilateral $S_{ROI} + C_{ROI}$ region had larger translation errors than the C_{ROI} region alone in the AP direction [14]. The setup errors of breast radiotherapy were related to factors such as immobilization device, patient posture, radiotherapist experience and patient body mass index [15–19]. Therefore, it is necessary to use various methods to improve treatment accuracy, such as using X-ray image guidance, modifying the immobilization device, adding additional skin markers [6, 18, 20] and using optical surface imaging guidance to set up and correct posture errors in real time [21–23].

In some centres, the thoracic vertebral bone is considered as the position surrogate in thoracic cancer radiotherapy. To verify whether the thoracic vertebral bone can be a position surrogate in PMRT, we analysed the correlation and difference of the setup errors between the T_{ROI} and the C_{ROI}, S_{ROI} and $S_{ROI} + C_{ROI}$ regions. The results showed that the thoracic vertebral bone and other ROIs have no significant correlation but do have considerable differences (the maximum random error was 8.9 mm, and the corresponding PTV margin was >20 mm; see Table 3). Meanwhile, there was significantly less consistency in the registration results between T_{ROI} and C_{ROI} or S_{ROI} on any translational axis. All of these results indicate that the thoracic vertebral bone should not be used as a position surrogate in breast cancer radiotherapy.

Local setup errors in sub-regions are an important source of error [24] and can be evaluated through the ROIs of sub-regions in CBCT image guidance, but they are hard to correct online. In routine CBCT-guided practice, image registration is performed using $S_{ROI} + C_{ROI}$ as a whole ROI. In our study, the Bland–Altman analysis revealed good agreement in registration results between C_{ROI} and $S_{ROI} + C_{ROI}$ and between S_{ROI} and $S_{ROI} + C_{ROI}$. This means that using $S_{ROI} + C_{ROI}$ as a whole ROI is reasonable and acceptable in clinical practice. However, when using $S_{ROI} + C_{ROI}$ as a single ROI, the local setup errors of the C_{ROI} region ranged from 1.19 to 3.00 mm, and the corresponding PTV margins were 5.80, 4.82 and 6.50 mm in the ML, SI and AP directions, respectively. The local setup errors of the S_{ROI} region ranged from 0.77 to 2.65 mm, with 4.59, 4.73 and 3.47 mm PTV margin in the ML, SI and AP directions, respectively. This indicated that a

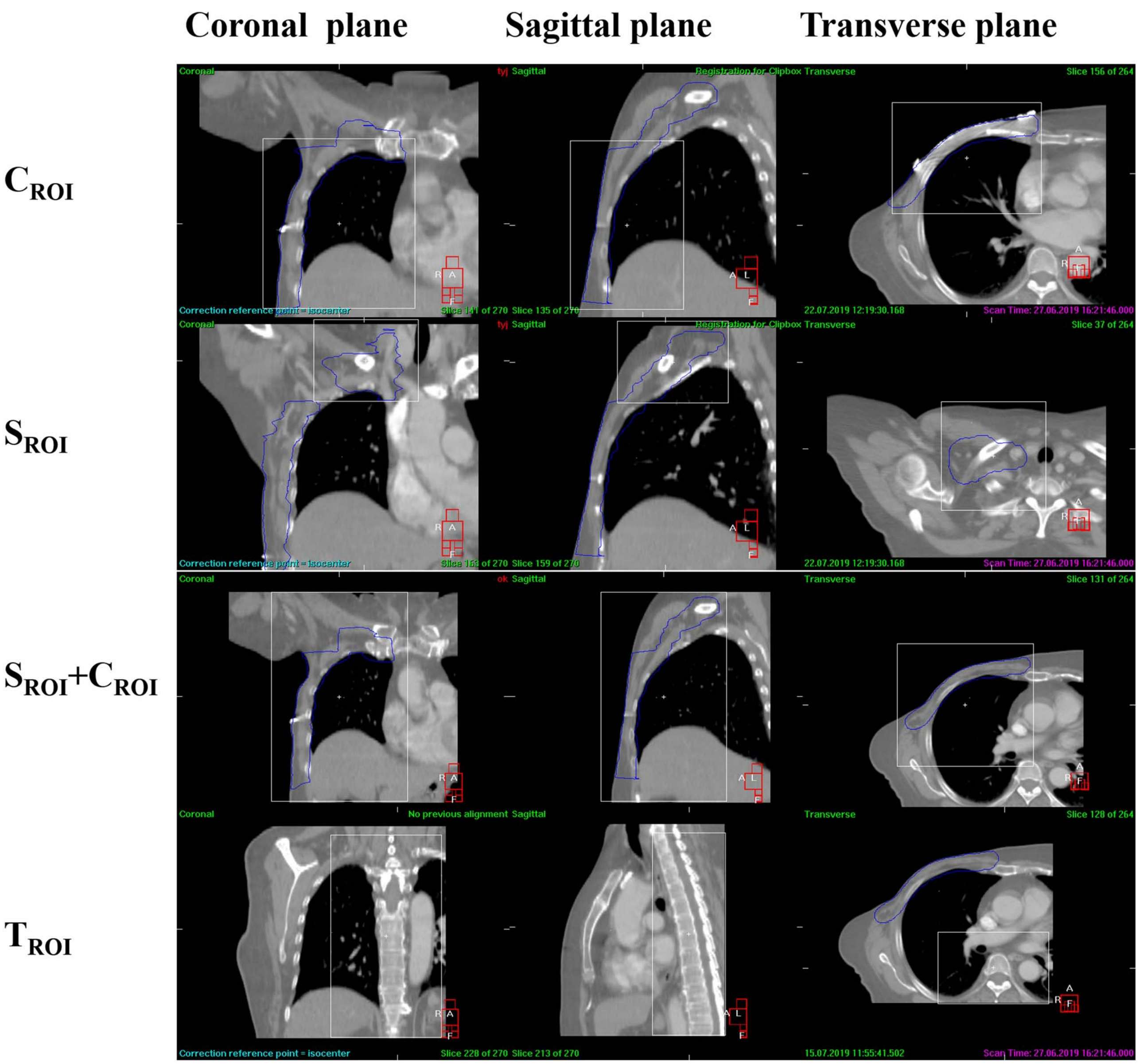

Fig. 2. Four sub-regions of interest (ROI) for the local setup error analysis in the same patient. Rows represent the ipsilateral chest wall region (C_{ROI}), the supraclavicular region (S_{ROI}), the ipsilateral chest wall plus supraclavicular region ($S_{ROI} + C_{ROI}$) and the vertebral region (T_{ROI}). Columns represent coronal planes, sagittal planes and transverse planes.

PTV margin of 5 mm can cover the local setup errors of the S_{ROI} region. Meanwhile, to compensate for the local setup errors of the C_{ROI} region, a 7-mm PTV margin is required, even with CBCT guidance. However, considering the buildup effect, the thickness of the chest wall and the dose limitations of the lung and heart, a smaller PTV margin is preferred for PMRT. In other words, the larger PTV margin would increase the dose coverage of the target but compromise the dose limitation of organs at risk. Meanwhile, the dose coverage of the target using a complete IMRT plan is more sensitive to setup errors than using a field-in-field plan [5]. Therefore, more caution should be used when using an IMRT plan if there are larger setup errors. Furthermore, a more effective immobilization method for PRMT is urgently required.

It is worth noting that the margin calculation by van Herk [11] was used only for translational errors. In the larger target region such as the $S_{ROI} + C_{ROI}$ region, even small rotational errors may result in dose uncertainty [25]. In clinical practice, it is difficult to correct the rotation errors and local setup errors using CBCT image guidance. Fortunately, the optical surface guiding system can be used to adjust the posture of the patient and reduce rotational and local setup errors. Meanwhile, to cover the intrafractional error (mainly considering the patient's respiratory motion for PMRT), we should consider the internal margin (IM) in the PTV margin. In our institution, we placed six metal markers on the patient's chest wall and measured the respiratory motion using fluoroscopy for another 20 patients (unpublished results). We found that

Table 1. Multiple comparisons between groups [Games-Howell (A)*, *P*-value]

	S_{ROI}	C_{ROI}	$S_{ROI}+C_{ROI}$	T_{ROI}		S_{ROI}	C_{ROI}	$S_{ROI}+C_{ROI}$	T_{ROI}
ML					Pitch				
S_{ROI}		0.96	0.98	0.26	S_{ROI}		1.00	0.67	0.14
C_{ROI}	0.96		0.82	0.57	C_{ROI}	1.00		0.74	0.15
$S_{ROI}+C_{ROI}$	0.98	0.82		0.13	$S_{ROI}+C_{ROI}$	0.67	0.74		0.59
T_{ROI}	0.26	0.57	0.13		T_{ROI}	0.14	0.15	0.59	
SI					Roll				
S_{ROI}		1.00	0.98	0.51	S_{ROI}		0.11	0.44	0.01
C_{ROI}	1.00		0.99	0.59	C_{ROI}	0.11		0.80	0.70
$S_{ROI}+C_{ROI}$	0.98	0.99		0.73	$S_{ROI}+C_{ROI}$	0.44	0.80		0.18
T_{ROI}	0.51	0.59	0.73		T_{ROI}	0.01	0.70	0.18	
AP					Yaw				
S_{ROI}		0.01	0.51	0.54	S_{ROI}		0.00	0.00	0.00
C_{ROI}	0.01		0.18	0.00	C_{ROI}	0.00		0.00	0.23
$S_{ROI}+C_{ROI}$	0.51	0.18		0.05	$S_{ROI}+C_{ROI}$	0.00	0.00		0.23
T_{ROI}	0.54	0.00	0.05		T_{ROI}	0.00	0.23	0.23	

*Multiple comparisons between the registration results of four ROIs were done by using the Games-Howell procedure. A *P* value of 0.05 was considered statistically significant.

Table 2. Correlation of setup errors in difference region

	S_{ROI}	C_{ROI}	$S_{ROI}+C_{ROI}$	T_{ROI}		S_{ROI}	C_{ROI}	$S_{ROI}+C_{ROI}$	T_{ROI}
ML					Pitch				
S_{ROI}	1.00	0.80**	0.89**	−0.06	S_{ROI}	1.00	0.28**	0.50**	−0.02
C_{ROI}	0.80**	1.00	0.87**	−0.02	C_{ROI}	0.28**	1.00	0.62**	−0.13**
$S_{ROI}+C_{ROI}$	0.89**	0.87**	1.00	−0.04	$S_{ROI}+C_{ROI}$	0.50**	0.62**	1.00	−0.17**
T_{ROI}	−0.06	−0.02	−0.04	1.00	T_{ROI}	−0.02	−0.13**	−0.17**	1.00
SI					Roll				
S_{ROI}	1.00	0.85**	0.87**	−0.06	S_{ROI}	1.00	0.20**	.61**	−0.07
C_{ROI}	0.85**	1.00	0.89**	−0.06	C_{ROI}	0.20**	1.00	.39**	0.02
$S_{ROI}+C_{ROI}$	0.87**	0.89**	1.00	−0.10**	$S_{ROI}+C_{ROI}$	0.61**	0.39**	1.00	−0.04
T_{ROI}	−0.06	−0.06	−0.10**	1.00	T_{ROI}	−0.07	0.02	−0.04	1.00
AP					Yaw				
S_{ROI}	1.00	0.86**	0.92**	−0.25**	S_{ROI}	1.00	0.27**	.65**	−0.06
C_{ROI}	0.86**	1.00	0.084**	−0.25**	C_{ROI}	0.27**	1.00	.58**	−0.08
$S_{ROI}+C_{ROI}$	0.92**	0.84**	1.00	−0.30**	$S_{ROI}+C_{ROI}$	0.65**	0.58**	1.00	−0.08
T_{ROI}	−0.25**	−.25**	−0.30**	1.00	T_{ROI}	−0.06	−0.08	−0.08	1.00

**The correlation was statistically significant, $P = 0.01$, two tails.

the average motion was ∼1 mm in all translational directions (ranging from 0 to 1 mm in the ML direction, 0 to 2 mm in the SI direction and 0 to 4 mm in the AP direction). The results were consistent with the report by Harris *et al.* [26]. Furthermore, in the CBCT image, we did not find image blur in the chest wall caused by respiratory motion. Michalski *et al.* [5] reported that interfraction motion has a larger effect on dose distributions than intrafraction motion. According to these findings, we believe that we can ignore the IM or consider only a 1 mm IM for PMRT.

There are some limitations in this study. First, this was the first single-institution study of local setup errors in PMRT patients immobilized with a CIVCO Breast Board Cushion, so it is difficult to tell whether these results are large or small. Second, the size of the CIVCO Breast Board Cushion is too small to adequately indicate the position of the patient's head, arms and body, which may reduce the reproducibility of the patient's position. Third, the low-dose CBCT scan mode (small field of view, low kV and low milliampere seconds (mAS)) was used, resulting in poor quality of the CBCT and a small image field. Therefore, we cannot use these CBCT images to recalculate the actual dose distribution and analyse the position of the heart. In the future, more effective immobilization, the optical surface guiding system and actual dose distribution should be studied.

This study confirmed that there are large setup errors and local setup errors in PMRT patients immobilized with the CIVCO vacuum bag. Thus, a more effective immobilization device and image guidance are urgently required. The vertebral body should not be the position

Table 3. The registration results in different ROIs and the difference of these errors among ROIs

ROIs	Local setup errors	Directions		
		ML	SI	AP
S_{ROI}	Σ	3.30	3.10	4.34
	σ	3.51	4.52	4.30
	Margin (mm)	10.71	10.91	13.87
C_{ROI}	Σ	3.81	3.61	4.40
	σ	3.53	4.78	4.64
	Margin (mm)	12.00	12.37	14.25
$S_{ROI} + C_{ROI}$	Σ	3.27	3.21	4.01
	σ	3.52	4.67	4.26
	Margin (mm)	10.64	11.29	13.00
T_{ROI}	Σ	1.65	2.24	2.42
	σ	4.98	5.85	7.04
	Margin (mm)	7.62	9.70	10.97
S_{ROI}-T_{ROI}	Σ	4.24	4.34	6.29
	σ	6.01	7.39	8.65
	Margin (mm)	14.81	16.02	21.76
C_{ROI}-T_{ROI}	Σ	4.59	4.82	6.36
	σ	5.86	7.53	8.90
	Margin (mm)	15.59	17.31	22.13
($S_{ROI} + C_{ROI}$)-T_{ROI}	Σ	4.19	4.50	6.07
	σ	5.90	7.63	8.85
	Margin (mm)	14.59	16.60	21.38
($S_{ROI} + C_{ROI}$)-S_{ROI}	Σ	1.29	1.15	0.77
	σ	1.96	2.65	2.20
	Margin (mm)	4.59	4.73	3.47
($S_{ROI} + C_{ROI}$)-C_{ROI}	Σ	1.81	1.19	1.76
	σ	1.84	2.64	3.00
	Margin (mm)	5.80	4.82	6.50

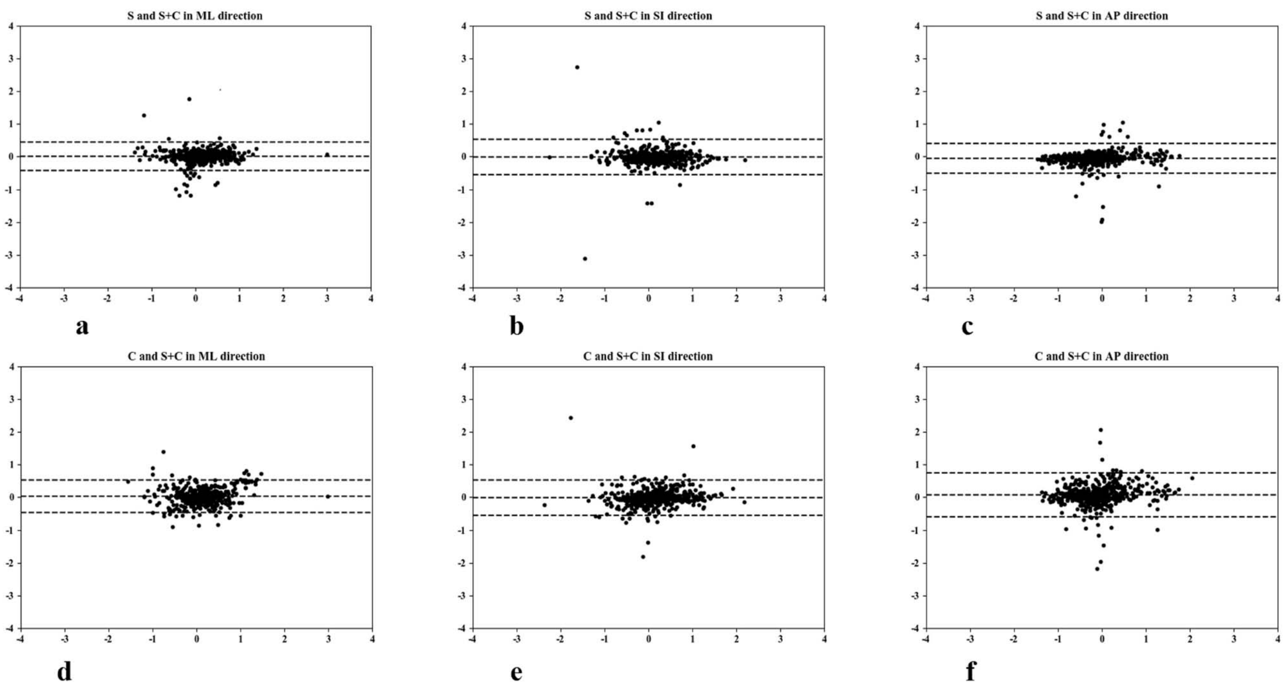

Fig. 3. Bland–Altman error analysis for the S_{ROI} and C_{ROI} vs $S_{ROI} + C_{ROI}$ registration results in translational directions. (a), (b) and (c) S_{ROI} vs $S_{ROI} + C_{ROI}$ registration results in the ML, SI and AP directions, respectively. (d), (e) and (f) C_{ROI} vs $S_{ROI} + C_{ROI}$ registration results in the ML, SI and AP directions, respectively. The abscissa indicates the mean registration results and the ordinate indicates the difference between registration results. The upper and lower dashed black lines are the 95% confidence interval. The middle dashed black line is the mean of the difference. The number of points exceeding the 95% confidence interval was <24 (5% of the total registration number 473), which indicated that the S_{ROI} and $S_{ROI} + C_{ROI}$, C_{ROI}, and $S_{ROI} + C_{ROI}$ have strong registration consistency.

surrogate for the supraclavicular region or chest wall. To compensate for the local setup errors of the chest wall or supraclavicular area, different PTV margins are required, even with CBCT guidance.

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CONFLICT OF INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

J.Z. and S.L. collected data and drafted the manuscript. C.Y., K.S., A.L., G.C., X. L. and W.W. helped to collect the data. S.B. helped to design the study. R.Z. designed the study, and revised and approved the final manuscript. All authors read and approved the manuscript.

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