

# Study to Compare the Effect of Different Registration Methods on Patient Setup Uncertainties in Cone-beam Computed Tomography during Volumetric Modulated Arc Therapy for Breast Cancer Patients

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## Abstract

**Purpose:** This study compared three different methods used in registering cone-beam computed tomography (CBCT) image set with planning CT image set for determining patient setup uncertainties during volumetric modulated arc therapy (VMAT) for breast cancer patients. **Materials and Methods:** Seven breast cancer patients treated with 50 Gy in 25 fractions using VMAT technique were chosen for this study. A total of 105 CBCT scans were acquired by image guidance protocol for patient setup verification. Approved plans' CT images were used as the reference image sets for registration with their corresponding CBCT image sets. Setup errors in mediolateral, craniocaudal, and anteroposterior direction were determined using gray-scale matching between the reference CT images and onboard CBCT images. Patient setup verification was performed using clip-box registration (CBR) method during online imaging. Considering the CBR method as the reference, two more registrations were performed using mask registration (MR) method and dual registration (DR) (CBR + MR) method in the offline mode. For comparison, systematic error ( $\Sigma$ ), random error ( $\sigma$ ), mean displacement vector ( $R$ ), mean setup error ( $M$ ), and registration time ( $R_t$ ) were analyzed. *Post hoc* Tukey's honest significant difference test was performed for multiple comparisons. **Results:** Systematic and random errors were less in CBR as compared to MR and DR ( $P > 0.05$ ). The mean displacement error and mean setup errors were less in CBR as compared to MR and DR ( $P > 0.05$ ). Increased  $R_t$  was observed in DR as compared to CBR and MR ( $P < 0.05$ ). In addition, multiple comparisons did not show any significant difference in patient setup error ( $P > 0.05$ ). **Conclusion:** For breast VMAT plan delivery, all three registration methods show insignificant variation in patient setup error. One can use any of the three registration methods for patient setup verification.

**Keywords:** Breast cancer, clip-box, cone-beam computed tomography, mask, random error, systematic error, volumetric modulated arc therapy

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## INTRODUCTION

Volumetric modulated arc therapy (VMAT) has been used for different clinical sites in external beam radiotherapy (EBRT). It has many advantages such as rapid treatment delivery and highly conformal dose distribution.<sup>[1]</sup> For the successful delivery of this highly conformal VMAT technique, the patient setup error needs to be minimized before treatment execution. Patient positioning is very important to increase the accuracy of target localization and reduce toxicity to critical organs. There are many factors that lead to uncertainties in the positioning of the target volume.<sup>[2]</sup> Postmastectomy chest wall (CW) VMAT

delivery is a challenging task during patient setup due to the thin and curved CW, skin folds, surrounding organ at risk (OAR) volume, breathing in motion, and location of noncoplanar supraclavicular and auxiliary nodes. Hence, image-guided radiation therapy (IGRT) is necessary to minimize patient

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setup errors in translation and rotation before each fraction of the treatment.<sup>[3,4]</sup> Linear accelerator (linac) equipped with onboard cone-beam computed tomography (CBCT) provides three-dimensional (3D) reconstructed images for improving patient position accuracy. Hui-Juan *et al.* compared setup error using CBCT for modified radical mastectomy (MRM) patients between single CW radiotherapy (RT) and CW with the supraclavicular region (SR). The study reported that positioning errors with daily image guidance of MRM patients should be checked and corrected.<sup>[5]</sup>

3D-CBCT images can offer better views of soft tissue, anatomical contrast, and accuracy as compared to two-dimensional (2D) images.<sup>[6,7]</sup> Hawkins *et al.* compared setup error variation between CBCT image and electronic portal imaging (EPI) for esophageal cancers. The study results showed that CBCT verification offers adequate 3D volumetric image quality to improve the accuracy of the treatment delivery and should be used for image guidance.<sup>[6]</sup> Topolnjak *et al.* quantified the difference in setup error measured with CBCT and EPI using bony anatomy matching in breast cancer. The results revealed that EPI registration underestimated the actual bony anatomy by 20%–50% and CBCT decreased setup uncertainties significantly.<sup>[7]</sup> Similarly, Batumalai *et al.* compared setup errors between EPI and CBCT imaging methods for patients undergoing tangential breast RT. The CBCT and EPI showed insignificant variation in their ability to detect setup error, suggesting that both methods are equal.<sup>[4]</sup>

The accuracy of the patient setup error is based on the registration method and the algorithm used in CBCT. Studies have been conducted on different registration methods for various clinical sites.<sup>[8,9]</sup> Campbell *et al.* assessed the accuracy and consistency of automated soft-tissue localization between manual soft-tissue registration and dual registration (DR) tool. The results revealed that both methods being tested produced clinically acceptable results. An increased variance was seen in the anteroposterior (AP) direction where the bladder and the rectal filling were involved.<sup>[10]</sup> Similarly, Goldsworthy *et al.* evaluated the impact of standard clip-box registration (SCR) and DR based on a clinical judgment for oropharyngeal cancer. They reported that DR was an effective IGRT tool to ensure target coverage of inferior neck nodes as compared to SCR and have demonstrated acceptability to RT clinical practice.<sup>[11]</sup>

There is no precise data available for the evaluation of the three different registration methods provided by Elekta in their linacs for 3D X-ray volumetric imaging (XVI). The aim of the present study was to evaluate the three different registration methods used in Elekta's XVI system on the estimation of patient geometrical uncertainties in the treatment of MRM breast cases by VMAT.

## MATERIALS AND METHODS

### Patient selection and planning

Seven post-MRM breast cancer patients who were treated with 50 Gy in 25 fractions were chosen for this study. VMAT

plans were generated using 6 MV photon beams. Patients were imaged with CBCT on alternate days during their course of treatment. In all, 15 CBCT image sets were acquired for each patient for 5 weeks. The total image sets thus obtained were 105. A total of 315 registrations were performed using three registration methods for patient setup error. Patients were positioned supine using breast board, headrest, and both arms raised above their head holding hand grip and arm support. In addition, a vacuum cushion (Orfit industries, Wijnegem, Belgium) was used for immobilization supported by indexing bar in the carbon fiber tabletop (Qfix, PA, USA). A thickness of 5 mm bolus was added to the patient CW. To identify the surgical scar, a radiopaque lead wire was placed on the skin surface. Three fiducial markers were placed on the patient's body with the support of laser alignment for isocenter reference. The patient simulation was performed during free breathing using positron emission tomography-CT (Biograph Truepoint<sup>®</sup> HD, Siemens Medical solution, PA, USA) simulator. CT slice thickness of 2 mm was used for delineation of the targets and OAR as per the International Commission on Radiation Units and Measurements (ICRU) 50/62/83 recommendations using Monaco<sup>™</sup> TPS V5.1 (IMPAC Medical System, Inc., Maryland Heights, MU, USA) treatment planning system (TPS).<sup>[12-14]</sup> All the VMAT plans were approved by a radiation oncologist and transferred from TPS to CBCT system along with the corresponding planning CT datasets to be used as the reference image data sets.

### Cone-beam computed tomography image acquisition

XVI system together with Elekta Synergy<sup>®</sup> (Elekta Ltd, Crawley, UK) linear accelerator was used as the IGRT system to acquire onboard CBCT images before patient treatment delivery. It consisted of kilo-voltage X-ray source arm and amorphous silicon flat panel imager. Patient's 3D-CBCT images acquired at isocenter were as per the scanning protocol recommended by the vendor. The image acquisition parameters were 120 kV, 528 mA, clockwise gantry rotation from 180° to 180°, fast scan, gantry speed 360°/min, collimator cassette M20, F1 filter, and 330 frames. XVI software version 5.0.2 was used for the reconstruction of CBCT images with 0.2 cm resolution in all dimensions.

### Cone-beam computed tomography VolumeView<sup>™</sup> and image matching

The acquired XVI sequence of 2D projection images were used to reconstruct a 3D image. This 3D volume view was registered with the reference CT image to calculate the positional shifts of the patient. Feldkamp's back-projection algorithm was used for image reconstruction optimization. The XVI release V5.0.2 software has an option to choose from different registration methods, namely manual, bone ( $T + R$ ), gray value ( $T + R$ ), and gray value ( $T$ ) to match reference CT images with onboard CBCT images where  $T$  and  $R$  represent the 3D translation and rotation error. The manual matching required significantly more time as compared to automatic matching.<sup>[15]</sup> The gray value ( $T + R$ ) registration algorithm used gray value "correction ratio" procedure for automatic registration. The gray value

intensity matching of the voxels in the registration volume was performed during the registration process. Among bone and gray automatic matching, the gray value matching was found to be superior.<sup>[16]</sup>

### Gray value ( $T + R$ ) automatic matching

The gray value ( $T + R$ ) automatic image matching method was used in the present study to evaluate the patient treatment setup error. The patient positional errors in the mediolateral (ML), craniocaudal (CC), and AP directions were recorded as X, Y, and Z translational errors. The maximum tolerance limits for translational and rotational errors were fixed at 3 mm and 1°, respectively, in any direction. In the present study, we did not use rotational errors for comparison and patients were repositioned if the errors were larger than 1° and a repeat CBCT was performed.

### Three registration methods

There are three types of registration methods used in gray value ( $T + R$ ) automatic matching in XVI, which are as follows:

1. Clip-box registration (CBR): In this method, a volume of interest is defined on the CT image in the form of a box drawn on the axial, coronal, and sagittal views around the anatomy of interest. The dimensions of the box are user definable. The registration between image sets is limited only to the voxels within the clip box which contains the target volume. It is a rigid registration process and does not include any margins during image matching. Chamfer algorithm is used for image matching
2. Mask registration (MR): Image registration using a soft-tissue volume is called as MR. The mask sets an irregular 3D region of interest around any chosen volume. The registration is again limited only to the voxels inside this volume which must include the target volume as shown in Figure 1. In addition, MR has an option to choose differential margins in each direction by the user
3. DR (clip box + MR or DR): DR is defined as the combination of CBR and MR registrations. The average of the errors determined from these two registrations is considered as the final patient setup error as shown in Figure 2.

### Implementation of registration methods

As per the Radiation Therapy Oncology Group guidelines, clinical target volume (CTV) was delineated for CW, internal mammary nodes (IMN), axillary region (AR), and SR.<sup>[17]</sup> Suitable margins around CTV were defined to construct the planning target volume (PTV) accounting for both internal and external patient setup uncertainties according to the ICRU report 83. The OAR volumes such as heart, bilateral lungs, contralateral breast, humeral head (ipsilateral), esophagus, and spinal cord were contoured by an experienced radiation oncologist. The CBR setting was performed around the whole PTV volumes which included CW, IMN, AR, and SR in the coronal, sagittal, and axial plane as shown in Figure 3. The MR setting was done on the whole PTV volume with 3-mm margin in all directions as shown in Figure 1. In DR methods,

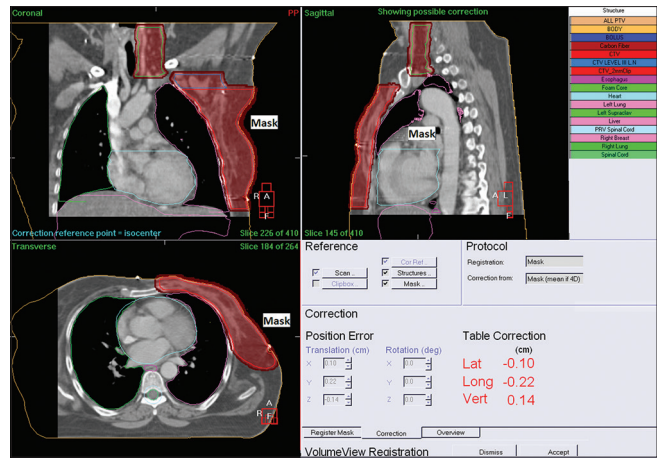


Figure 1: Mask registration method on three different planes

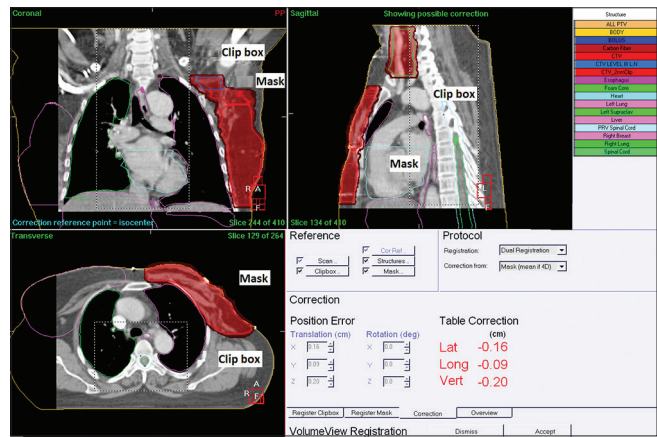


Figure 2: Dual registration method (clip-box + mask) on three different planes

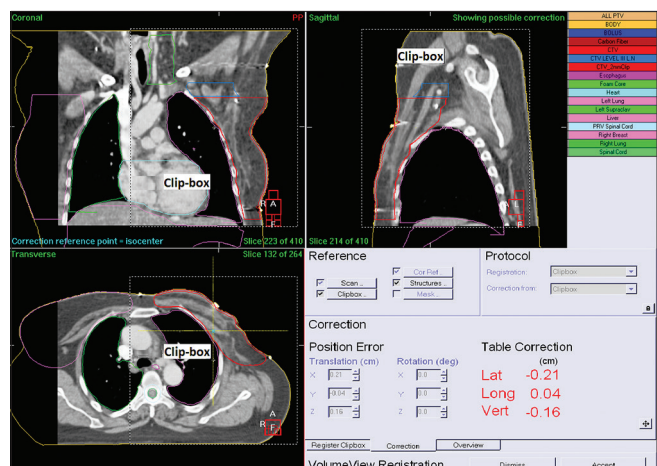


Figure 3: Clip-box registration method on three different planes

CBR and MR settings were performed to the spinal cord and whole PTV in three planes as shown in Figure 2. Automatic registrations were performed between reference CT images and onboard CBCT images to determine patient setup errors. The final patient setup errors were determined based on image matching and clinical decision.

The errors were corrected online by performing table correction using “convert correction” option in the XVI software. The image matching was performed by a radiotherapist, verified by a senior radiotherapist, and finally approved by a radiation oncologist for treatment delivery. For the present study, only CBR registration method was performed before treatment delivery. Considering CBR as a reference, the other two registration methods were performed in the offline mode for comparison.

**Patient setup errors ( $\mu$ )**

The patient setup deviation is defined as the difference between the actual and intended position of the part of the patient’s body to be irradiated. The intended position is recorded on a reference image.

Setup errors are separated into two main classes: (1) systematic error and (2) random error.

1. Systematic error ( $\Sigma$ ): Systematic errors are deviations between the planned patient position and the average position over a course of the fractionated therapy. The systematic error for a population of patients is calculated as the standard deviation of mean errors for each patient using three different registration methods<sup>[18,19]</sup>
2. Random error ( $\sigma$ ): Random errors are deviations between different fractions, during a treatment series. It is computed as the root mean square value of the standard deviation of errors recorded for each patient using three different registration methods.<sup>[20-22]</sup>

**Mean displacement vector ( $R$ )**

The mean displacement vector is one whose length is the shortest distance from the initial to the final position of a point. It is quantified as both distance and direction of the patient setup error. The length of the patient translation errors was computed as follows:<sup>[21]</sup>

$$R = \sqrt{(d_{ML}^2 + d_{CC}^2 + d_{AP}^2)}$$

where,  $d_{ML}$ ,  $d_{CC}$ , and  $d_{AP}$  are deviations in ML, CC, and AP directions, respectively.

**Mean setup error**

The mean setup error ( $M$ ) is defined as the average of setup errors in each direction.<sup>[21]</sup>

**Intrafractional setup error**

Intrafractional error is defined as the errors caused by organ motion or patient position change during treatment delivery. The difference between post correction CBCT and post-treatment CBCT could be regarded as intrafractional errors.<sup>[23]</sup>

**Registration time ( $R_i$ )**

The registration time is calculated using a stopwatch for individual methods to evaluate their efficiency. The difference between start and end time is called registration time ( $R_i$ ).<sup>[22,24]</sup>

$R_i = R_{ST} - R_{ET}$  where  $R_{ST}$  and  $R_{ET}$  represent the start and end time of registration,

**Statistical analysis**

The statistical analysis was performed on three different registration methods using the one-way ANOVA followed by *post hoc* analysis using Tukey’s honestly significant difference (HSD) test ( $P < 0.05$ ) to determine the  $P$  value of the analyzed data using SPSS software (SPSS V.16, IBM, IL, USA).

**RESULTS**

The final results showed some similarities and differences in setup errors due to the influence of different registration methods. They were evaluated using descriptive and inferential statistics and represented using tables and figures.

Table 1 shows the results of systematic ( $\Sigma$ ) and random error ( $\sigma$ ) of the couch direction in all three directions. The systematic and random errors for CBR were as follows: in ML direction,  $\Sigma = 3.2$  mm and  $\sigma = 2.5$  mm; in CC direction,  $\Sigma = 2.6$  mm and  $\sigma = 2.0$  mm; and in AP direction,  $\Sigma = 2.7$  mm and  $\sigma = 1.9$  mm. Similarly, systematic and random errors for MR in ML direction were  $\Sigma = 3.4$  mm and  $\sigma = 2.7$  mm; in CC direction  $\Sigma = 3.1$  mm and  $\sigma = 2.3$  mm; and in AP direction  $\Sigma = 2.7$  mm and  $\sigma = 2.1$  mm. The systematic and random errors for DR in ML direction were  $\Sigma = 3.7$  mm and  $\sigma = 2.9$  mm; in CC direction  $\Sigma = 3.0$  mm and  $\sigma = 2.4$  mm; and in AP direction  $\Sigma = 2.7$  mm and  $\sigma = 2.0$  mm. The CBR method showed marginally less setup error as compared to MR and DR ( $P > 0.05$ ). No significant differences were observed among three registration methods ( $P > 0.05$ ).

The mean setup errors for CBR, MR, and DR in ML direction (−0.13 mm, 0.23 mm, and 0.01 mm), in CC direction (−0.01 mm, 0.93 mm, and −0.06 mm), and in AP directions (0.64 mm, 2.30 mm, and 0.29 mm) were observed. The mean setup error was slightly higher in MR registration as compared to CBR and DR as shown in Figure 4. No significant differences were observed among the three registration methods ( $P > 0.05$ ). Similarly, the results of the mean displacement vector were marginally less in CBR as compared to MR and DR methods as shown in Figure 5. Statistically insignificant results were observed among three methods ( $P > 0.05$ ).

Multiple comparisons were done among CBR-MR, CBR-DR, and MR-DR in ML, CC, and AP direction using *post hoc*

**Table 1: Systematic ( $\Sigma$ ) and random ( $\sigma$ ) errors calculated for three different registration methods**

Category	n	Systematic error (mm)			Random error (mm)		
		X (ML)	Y (CC)	Z (AP)	X (ML)	Y (CC)	Z (AP)
CBR	105	3.2	2.6	2.7	2.5	2.0	1.9
MR	105	3.4	3.1	2.7	2.7	2.3	2.1
DR (CBR + MR)	105	3.7	3.0	2.7	2.9	2.4	2.0

X (ML): X Mediolateral, Y (CC): Y Craniocaudal, Z (AP): Z Anteroposterior, CBR: Clip-box registration, MR: Mask registration, DR: Dual registration, systematic ( $\Sigma$ ) error, random ( $\sigma$ ) errors

Tukey’s HSD test as shown in Table 2. The results revealed that significant differences were observed in CBR-MR and MR-DR methods in AP direction ( $P < 0.05$ ). On the other hand, no significant differences were observed for ML and CC directions ( $P > 0.05$ ).

The registration time for CBR, MR, and DR methods were  $0.57 \pm 0.44$  min,  $0.59 \pm 0.46$  min, and  $1.58 \pm 0.75$  min, respectively. The CBR and MR were almost similar with no significant differences ( $P > 0.05$ ). And, the time taken by DR methods was significantly higher as compared to the other two methods ( $P < 0.05$ ).

## DISCUSSION

Accurate patient positioning is one of the critical points in ensuring optimal clinical outcomes. It would allow to have tighter CTV-to-PTV margins, thus making possible dose escalation to PTV and reduced normal tissue complication rates.<sup>[19,20]</sup> Measurement and correction of intrafractional patient setup error before CBCT could improve the precision of the RT treatment delivery. The use of IGRT has been shown in many studies to result in reduced inter- and intrafractionation

uncertainties in patient’s setup error.<sup>[23,25,26]</sup> Conventional bony anatomy patient position verification protocols were inadequate as compared to CBCT in accounting for soft-tissue target and organ variation.<sup>[27]</sup> The CBCT image guidance was found to be better in image quality to improve the accuracy of treatment delivery in VMAT breast delivery and reduce setup uncertainties significantly.<sup>[5]</sup> The vendor release notes stated that they verified the registration accuracy of this algorithm in XVI on the phantom study. Therefore, for clinical use, it is necessary to validate registration accuracy for different clinical sites.<sup>[28]</sup>

Hawkins *et al.* evaluated the setup error for 20 esophageal cancer patients using CBR method for four different user-defined volumes such as carina, vertebrae, and thorax. The study results showed that the alignment of CB and registration method selected could have an effect on the displacements (translations and rotations) obtained.<sup>[8]</sup> In clinical use, the size of the clip box could vary according to clinical site and volume defined by the user. A study by Pohl *et al.* investigated the influence of the size of the clip box on patient setup error in prostate cancer using 46 CBCT images.

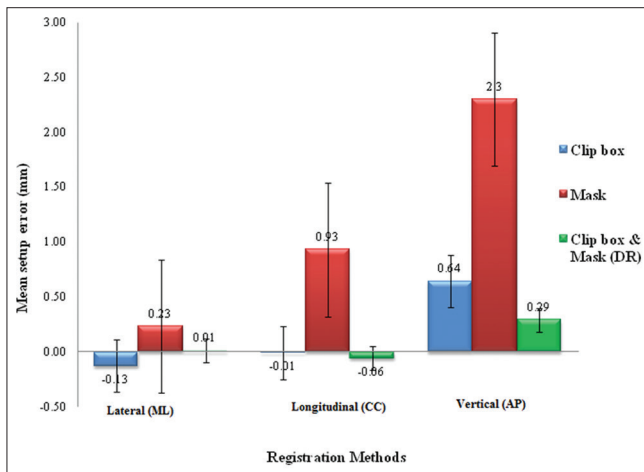


Figure 4: Comparison of mean setup error of three registration methods

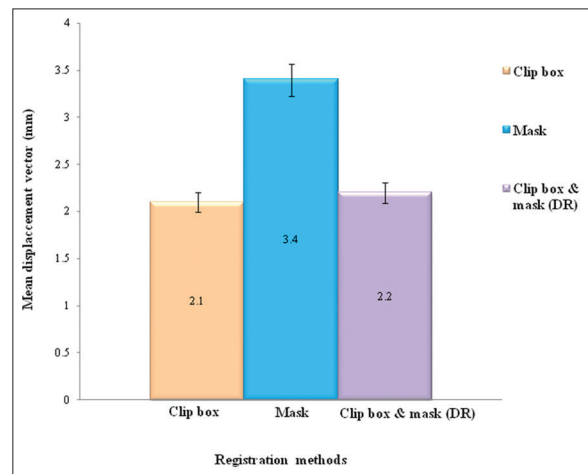


Figure 5: Comparison of mean displacement vector of three different registration methods

Table 2: Multiple comparisons of three different registration methods using *post hoc* Tukey’s honestly significant difference test

Translation errors	I method	J method	Mean difference (I–J) (mm)	SE (mm)	Significant	95% CI	
						Lower bound	Upper bound
X (ML)	CBR	MR	-0.360	0.620	0.827	-0.183	0.109
		CBR and MR (DR)	-0.130	0.620	0.974	-0.160	0.132
	MR	CBR and MR (DR)	0.220	0.620	0.928	-0.123	0.169
Y (CC)	CBR	MR	-0.950	0.440	0.080	-0.198	0.008
		CBR and MR (DR)	0.050	0.440	0.991	-0.098	0.109
	MR	CBR and MR (DR)	1.000	0.440	0.059	-0.002	0.204
Z (AP)	CBR	MR	-1.660*	0.480	0.002	-0.279	-0.052
		CBR and MR (DR)	0.350	0.480	0.745	-0.078	0.149
	MR	CBR and MR (DR)	2.010*	0.480	0.001	0.087	0.315

\*Mean difference is significant at the 0.05 level. X (ML): X Mediolateral, Y (CC): Y Craniocaudal, Z (AP): Z Anteroposterior, CBR: Clip-box registration, MR: Mask. registration, DR: Dual registration, CI: Confidence interval, SE: Standard error

The study reported that clip box size had insignificant variation in translation and significant variation in rotation values.<sup>[9]</sup> Li *et al.* compared the results of CBR using three different landmarks, namely spine, spine + internal target volume, and lung for 15 lung cancer patients using four-dimensional (4D) CBCT automatic registration. The study found that the translation shifts were similar in all the three approaches.<sup>[29]</sup>

In DR methods, CBR followed by MR was used for gross and fine alignments in automatic matching to ensure target position accuracy. It was helpful in assessing whether an adequate or reduced margin can be used for the target.<sup>[29,30]</sup> Esteban *et al.* compared CBR and DR registration methods for different locations of lung tumors (peripheral and central) based on the translation shift in 4D-CBCT for 29 patients treated with stereotactic body RT. The results showed that different registrations resulted in different registration precisions for peripheral and central tumors, being favorable in all cases for MR with a statistically significant difference.<sup>[30]</sup> There was no published literature comparing patient setup error based on the gray value matching using three different registration methods in breast RT. Therefore, the present study compared translation errors between the three registration methods in the estimation of setup corrections using CBCT images in breast VMAT treatment. The present study was designed on similar lines adopted by Goldsworthy *et al.* who compared CBR and DR in the treatment of oropharyngeal cancer.

The present study revealed that the comparison results of three registration methods did not show any statistically significant results in systematic error, random error, mean displacement vector, and mean setup error even though the volumes included in the registration were different in each method. Furthermore, the CRR results were marginally less as compared to DR and MR. Multiple comparisons for setup error found insignificant differences in ML and CC directions whereas significant differences were seen in CBR-MR and MR-DR methods in AP direction. For clinical use, the time taken by each registration method to complete the whole process without compromising registration accuracy is an important factor. The time efficiency for each registration depends on the size of the registration volume and efficiency of an algorithm which was used for registration. A study by Yan *et al.* investigated the registration efficiency with different size of image set volumes. Their results showed that a significant decrease in registration time was achieved by reducing the size of image sets.<sup>[24]</sup> In the present study, the time taken by CBR was less as compared to MR and DR methods. The lesser registration time of the CBR method is an advantage in a busy clinic. It can avoid additional patient setup errors and reduce patient waiting time on treatment couch during treatment delivery.

## CONCLUSION

It can be concluded that three registration methods did not show any statistically significant differences in their ability to detect patient setup error in translation for breast MRM-VMAT

delivery. The user can use any of the three registration methods for patient setup verification.

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## Conflicts of interest

There are no conflicts of interest.

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