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Set-up accuracy in megavoltage computed tomography-guided adjuvant breast radiotherapy: An analysis of differences between automatic registration and human observers

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ABSTRACT

OBJECTIVE: The objective of the study was to evaluate the agreement of set-up shift measurements obtained by the TomoTherapy automatic image-registration system, radiation therapists (RTTs), and physicians during adjuvant breast radiotherapy, and to investigate the effects of RTT number and target volume on positioning accuracy.

METHODS: This retrospective single-center study included 40 female breast cancer patients treated with adjuvant helical TomoTherapy under daily megavoltage computed tomography (MVCT) guidance. Set-up shifts in the lateral, longitudinal, vertical, and roll directions were analyzed over 1,200 treatment fractions. Pairwise comparisons among the TomoTherapy system, RTTs, and physicians were performed using paired t-tests or Wilcoxon signed-rank tests with Bonferroni correction. The effect of RTT number was evaluated using the Wilcoxon signed-rank test within subgroups, and that of clinical target volume (CTV)/boost volume using the Kruskal-Wallis test.

RESULTS: High agreement was observed among the TomoTherapy system, RTTs, and physicians. The largest mean difference between RTT and physician measurements was 1.56 mm and remained within the institutional 5-mm CTV-to-planning target volume margin. Although statistically significant differences were found in selected translational axes, RTT number and CTV/boost volume did not significantly influence set-up shift values.

CONCLUSION: Daily MVCT-guided TomoTherapy provides reliable and reproducible patient positioning. Standardized RTT-led image-guided workflows maintain clinically acceptable set-up accuracy regardless of RTT team size or target volume.

Keywords: Breast neoplasms; helical tomotherapy; image-guided; radiotherapy; radiotherapy setup errors.

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Breast cancer (BC) is the most prevalent malignancy among women worldwide, accounting for diagnoses in United States and serving as a leading cause of cancer-related mortality. In 2023, an estimated that 297,790 new invasive cases and 43,170 deaths were projected to occur the United States alone, with curative outcomes achievable in approximately 70–80% of patients diagnosed with early-stage, non-metastatic disease [1, 2]. Recent advancements in BC screening techniques, including mammography and genetic testing, have greatly enhanced early detection and contributed to improved survival rates [3]. The standard treatment for BC typical-

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ly comprises three main therapeutic modalities: Surgery, radiotherapy (RT), and systemic therapy. Adjuvant RT plays a critical role by targeting and eradicating residual tumor cells that may remain following surgical interventions, whether breast-conserving surgery (BCS) or mastectomy [4]. Over the decades, BC RT has evolved significantly, transitioning from two-dimensional techniques to three-dimensional conformal RT, followed by intensity-modulated RT and volumetric modulated arc therapy. These advancements have improved the precision of tumor targeting while minimizing radiation exposure to surrounding healthy tissues [5, 6]. In recent years, the integration of image-guided RT (IGRT) has further enhanced treatment accuracy by utilizing real-time imaging during therapy sessions. While IGRT has become a routine part of modern RT, this innovative technique also introduces several challenges that must be addressed to optimize its implementation and effectiveness [6, 7].

In the RT process, ensuring that the patient remains in a fixed and consistent position during each treatment session is crucial for accurately delivering radiation to the tumor area and minimizing the impact on surrounding healthy tissues [8]. Set-up refers to the process of positioning the patient correctly before RT to precisely direct the planned radiation dose to the tumor region [9]. During TomoTherapy-based IGRT, pretreatment megavoltage computed tomography (MVCT) images are registered with the planning CT to verify patient positioning and quantify set-up deviations [10, 11]. MVCT provides volumetric anatomical information and enables the calculation and correction of translational shifts and roll before treatment [11]. Given the critical importance of accurate positioning in RT, advancements in imaging technologies have made it possible to achieve even greater precision and reliability in treatment delivery. To the best of our knowledge, few studies have simultaneously compared automated registration, radiation therapist (RTT) assessment, and physician approval in daily MVCT-guided TomoTherapy breast RT.

The aim of our study is to ensure accurate treatment positioning and effective immobilization of female BC patients undergoing adjuvant therapy with a TomoTherapy device in our clinic. To achieve this, we compare the set-up shift values obtained from the TomoTherapy Accuray automatic image alignment system with those recorded by physicians and RTTs. This study includes three key comparisons: the first between the automatic image alignment system and the values determined by physicians, the second between the values recorded by physicians and those recorded by RTTs, and the third between the automatic image alignment system and RTTs. By conducting these detailed comparisons, we aim to gain a comprehensive understanding of the discrepancies or consistencies between the three sources of data. Identifying potential set-up variations through this multi-faceted analysis will allow us to address inaccuracies in positioning and enhance the reliability of our RT practices. This study emphasizes how accurate set-up procedures directly impact treatment accuracy and reduce risks to patient safety.

Highlight key points

- Daily MVCT ensured reproducible patient positioning during adjuvant breast radiotherapy.
- Automated and human set-up measurements showed excellent clinical agreement.
- RTT-led image guidance maintained positioning accuracy within institutional margins.
- Target volume size and RTT number were not associated with set-up accuracy.
- Standardized TomoTherapy workflows supported reliable treatment delivery.

MATERIALS AND METHODS

Study Design and Participants

This retrospective, single-center study included 40 female patients with BC who received adjuvant RT at our institution. Of these, five patients underwent mastectomy, while the remaining 35 received BCS. The average age of the patients was 53.3 years. In addition, 28 patients had cancer in the left breast, and 12 in the right breast. Patients were selected based on the inclusion criteria of receiving adjuvant RT with the TomoTherapy system (Accuray Inc., Sunnyvale, CA, USA). Contouring of the clinical target volume (CTV) and boost volumes was performed using established guidelines: The ESTRO consensus guideline for early-stage BC for BCS cases and the RTOG atlas for postmastectomy cases [12, 13]. This approach ensured precision and consistency in contouring across all patients. All treatments were supervised by physicians and delivered using the TomoTherapy system for each fraction. The study was approved by the Institutional Ethics Committee (Approval No: 2025/010.99/16/17, Date: May 27, 2025) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Equipment and Techniques

Daily MVCT imaging was performed before each fraction to verify treatment position and alignment. The TomoTherapy Accuray automatic image alignment system automatically calculated initial set-up shift values, including lateral, longitudinal, vertical, and roll directions, and these values were recorded. The automatic registration parameters used for this process were "Full Image Technique," "Standard Resolution," and "Translations+Roll" settings, ensuring consistency in the evaluation of patient positioning. Subsequently, RTTs reviewed the values suggested by the automatic system, made their adjustments, and recorded these adjustments separately. Following the RTTs, the physician conducted a final review of the patient's position, and the physician's approved shift values were determined. Both RTTs and physicians independently evaluated the MVCT images in three planes: Coronal, sagittal, and vertical (Fig. 1). Finally, patients were treated using the shift values approved by the physician. The study aimed to evaluate the alignment consistency between the measurements obtained by the TomoTherapy system, RTTs, and physicians to enhance treatment accuracy and reliability.

In addition, the number of RTTs involved in treating each patient was documented and analyzed. In this context, the number of RTTs per patient was categorized into two groups: "3 or fewer" and "4 or more," and the potential impact of RTT numbers on set-up shift values was evaluated. Similarly, CTV/boost volumes were categorized, and their potential impact on set-up shift values was also analyzed.

Data Collection

Data were collected for each treatment session, and set-up shift values were categorized by source: TomoTherapy system, RTTs, and physicians. Three comparisons were performed: system versus physician, physician versus RTT, and system versus RTT. All statistical comparisons were performed at the individual fraction level, comprising a total of 1,200 fractions from the 40 patients.

Statistical Analysis

The normality of data distribution was evaluated using the Shapiro–Wilk and Kolmogorov–Smirnov tests. For normally distributed data, paired t-tests were used, while Wilcoxon signed-rank tests were applied to non-normally distributed data. Because three pairwise comparisons were performed within each axis, a Bonferroni correction was applied, and an adjusted threshold of $p<0.017$ (0.05/3) was considered statistically significant for these comparisons. Within each RTT-number subgroup, pairwise comparisons were performed using the Wilcoxon-signed-rank test, and the relationship between CTV/boost volumes and set-up shifts was analyzed using the Kruskal-Wallis test. Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 27; IBM Corp., Armonk, NY, USA), and a significance level of $p<0.05$ was considered.

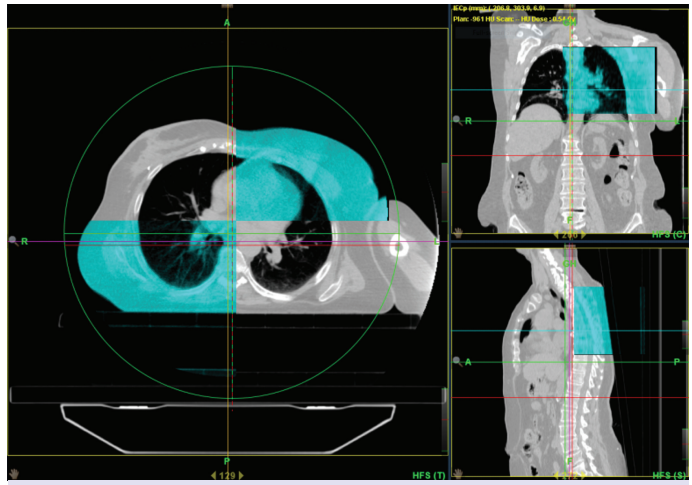

Figure 1. Representative registration of daily pretreatment megavoltage computed tomography (MVCT) with the planning CT during helical TomoTherapy. Axial (left), coronal (upper right), and sagittal (lower right) views are shown; the colored overlay depicts the registered comparison used for set-up verification.

RESULTS

Set-up shift values from all 1,200 treatment fractions were analyzed to provide a comprehensive overview of the data. To further evaluate the statistical properties of these values, the Shapiro–Wilk test was applied to assess the normality of the data distribution. Upon analysis, it was determined that, among the three groups (RTTs, Tomo, and physicians), the roll parameters did not meet the criteria for normal distribution, while the remaining parameters, including lateral, longitudinal, and vertical directions, demonstrated normal distribution. The mean differences between RTT and physician measurements across all four axes were as follows: 0.36 mm for the lateral axis, 0.98 mm for the vertical axis, 1.56 mm for the longitudinal axis, and 0.09° for the roll axis. These observations establish a robust statistical foundation, allowing for meaningful comparisons and detailed analyses to be conducted in the subsequent stages of this study (Table 1).

Table 1. Descriptive statistics and normality results for set-up parameters

Parameter	Mean value#	p	Parameter	Mean value#	p
rtt_lat	0.40	0.656	rtt_vert	8.40	0.328
tomo_lat	1.13	0.602	tomo_vert	8.59	0.393
dr_lat	0.76	0.803	dr_vert	9.38	0.245
rtt_long	-1.30	0.109	rtt_roll	-0.07	0.003*
tomo_long	-1.52	0.261	tomo_roll	-0.10	<0.001*
dr_long	-2.86	0.062	dr_roll	0.02	0.034*

#Mean values for the translational axes (lateral, longitudinal, and vertical) are expressed in millimeters (mm), whereas the roll parameter is a rotational displacement expressed in degrees (°). *Indicates a non-normal distribution (Shapiro-Wilk, p<0.05). RTT: Radiation therapist; tomo: TomoTherapy automatic registration; dr: Physician; lat: Lateral; vert: Vertical; long: Longitudinal.

Table 2. Statistical comparison table of set-up parameters

Comparison	Parameter	p	Comparison	Parameter	p
tomo_lat - dr_lat	Lateral	0.034	tomo_long - dr_long	Longitudinal	0.052
rtt_lat - tomo_lat	Lateral	<0.001*	rtt_long - tomo_long	Longitudinal	0.720
rtt_lat - dr_lat	Lateral	0.081	rtt_long - dr_long	Longitudinal	<0.001*
tomo_vert - dr_vert	Vertical	0.225	tomo_roll - dr_roll	Roll	0.549
rtt_vert - tomo_vert	Vertical	0.756	rtt_roll - tomo_roll	Roll	0.600
rtt_vert - dr_vert	Vertical	0.012*	rtt_roll - dr_roll	Roll	0.545

*Indicates statistical significance at the Bonferroni-adjusted threshold of p<0.017. RTT: Radiation therapist; tomo: TomoTherapy automatic registration; dr: Physician; lat: Lateral; vert: Vertical; long: Longitudinal.

Statistical comparisons revealed significant differences in specific parameters. For instance, in the lateral direction, tomo_lat showed significant differences when compared to rtt_lat but not dr_lat, whereas no significant difference was observed between rtt_lat and dr_lat, indicating consistency between rtt and dr measurements in this axis. In the vertical axis, although no significant differences were observed between tomo_vert and either rtt_vert or dr_vert, a notable difference was found between rtt_vert and dr_vert. Similarly, in the longitudinal axis, while there were no significant differences between tomo_long and either rtt_long or dr_long, rtt_long demonstrated a significant difference compared to dr_long. These findings emphasize the variability in set-up shift values across specific axes depending on the measurement source. The roll axis, however, did not show statistically significant differences between any of the groups. These results are summarized in Table 2, providing a detailed breakdown of the comparisons and their statistical significance.

During the treatment process, patients were grouped based on the number of different RTTs involved in their care. Patients treated by "3 or fewer RTTs" comprised 12 individuals, while those treated by "4 or more RTTs" comprised 28 individuals. Across all patients, the number of different RTTs per treatment ranged from a minimum of 1 to a maximum of 7. This grouping was used to evaluate the potential impact of RTT numbers on set-up accuracy. For each group, comparisons among tomo, rtt, and dr measurements were performed across four parameters (lateral, vertical, longitudinal, and roll). These comparisons were conducted using the non-parametric Wilcoxon signed-rank test. The tests evaluated differences between "tomo-rtt," "tomo-dr," and "rtt-dr" measurements for all axes separately within each group. The results of the analysis showed that, for both groups, no statistically significant differences were found in any of the four parameters (lateral, vertical, longitudinal, and roll). These findings suggest that the number of RTTs involved in the treatment process did not significantly

influence the consistency of measurements across the sources (tomo, rtt, and dr).

Kruskal–Wallis tests were conducted to evaluate the effect of CTV breast/chest wall and CTV boost volumes on set-up shift values. The results showed that these parameters did not have a statistically significant impact on set-up shift values ($p>0.05$). Furthermore, the analysis demonstrated that alignment consistency among tomo, RTT, and physician measurements was maintained across both breast/chest wall and boost volume categories.

DISCUSSION

The accuracy and consistency of set-up shift measurements among TomoTherapy (tomo), RTTs, and physicians in adjuvant BC RT were evaluated using MVCT-based image guidance across 1,200 treatment fractions. In addition, the influence of parameters such as RTT team size and CTV size on set-up accuracy was analyzed. These findings provide a comprehensive real-world understanding of alignment precision and inter-observer variability, highlighting the practical interplay between automated systems and human interpretation in modern IGRT workflows, and contextualizing their clinical significance through comparisons with existing literature. Although the automatic registration provided the initial alignment, the RTTs and physicians independently evaluated the MVCT images in three planes before approving the final shifts; the strong concordance observed among the three sources therefore reflects the reliability and reproducibility of this multi-observer verification workflow rather than a mere propagation of the automated result.

When comparing measurements between RTTs and physicians, the largest mean difference of 1.56 mm was observed in the longitudinal axis, while the smallest mean difference of 0.09° was found in the roll axis. These differences remain within the planning target volume (PTV) boundaries established in our clinic by applying a 5 mm margin around the CTV. In this context, clinical relevance is more important than statistical significance: Although statistically significant differences were observed in selected translational axes, the maximum mean discrepancy remained substantially below the institutional 5-mm planning margin and is therefore unlikely to affect treatment delivery. Previous studies have demonstrated that a 5 mm expansion from CTV to PTV is sufficient to compensate for set-up variability and ensure reliable dosimetry even under challenging conditions [14]. The findings of the current study are consistent with these results; all observed differences, including those in the roll and longitudinal axes, were within these margins. This further reinforces the robustness of the 5 mm PTV margin in compensating for systematic and random errors in BC RT [14, 15]. In addition, the effectiveness of these margins highlights that RTT-led set-up procedures can maintain alignment accuracy without the need for physician intervention. This ensures that the treatment target consistently remains within the planned RT field. The observed alignment precision underscores the importance of standardized protocols and their role in minimizing variability within clinical settings. Another important observation is that the number of RTTs involved in the treatment process did not significantly affect the set-up accuracy. When comparing patients treated by three or fewer RTTs versus those treated by four or more, no statistically significant differences were identified. This finding indicates that RTTs are adequately trained and demonstrate comparable expertise in operating the TomoTherapy device. Furthermore, this result aligns with the literature emphasizing the direct impact of RTT training and experience on RT accuracy [16]. The consistency observed across varying RTT numbers reflects the effectiveness of the clinic's training programs and the reliability of alignment protocols.

Previous breast RT studies have demonstrated that set-up accuracy may vary according to treatment position [17]. Daily orthogonal planar image-guided set-up in free-breathing patients has been shown to provide accurate tangential breast RT with few residual errors exceeding 5 mm [18]. Because residual geometric uncertainties may persist despite image verification, systematic PTV margins remain important for maintaining treatment accuracy [19]. More directly, MVCT-based image guidance in TomoTherapy enables the detection and correction of translational and roll deviations and has demonstrated millimetric set-up assessment with limited interobserver variability [10, 11]. These findings are consistent with the strong agreement observed among the automatic system, RTTs, and physicians in the present study. Despite this overall agreement, the roll measurements were non-normally distributed, although differences among the three measurement sources were not statistically significant. Residual set-up errors remain clinically relevant because translational shifts exceeding 5 mm or rotations exceeding 2° may produce clinically relevant dosimetric changes [20]. Simulated isocenter shifts

may also alter target coverage and doses to surrounding normal tissues, emphasizing the importance of accurate position verification [21]. Rotational set-up deviations can additionally be quantified using six-degree-of-freedom image-guidance approaches [22]. Therefore, careful evaluation of rotational alignment remains important. Standardized training and automated verification workflows may help reduce human error and improve consistency in RT procedures [23].

Particularly after BCS, post-operative seroma may cause clinically relevant changes in the tumor-bed and boost volume. In addition to set-up verification, pre-treatment MVCT may provide visual evidence of such anatomical changes and help identify cases in which adaptive replanning should be considered [24]. In the present study, no statistically significant association was detected between CTV/boost volume categories and set-up shift values. However, longitudinal anatomical changes and adaptive replanning were not evaluated.

This study has several limitations that should be considered when interpreting its findings. First, its retrospective, single-center design and relatively small sample size (40 patients) may limit the generalizability of the results to other institutions, patient populations, and treatment platforms. Nevertheless, setup accuracy was evaluated across 1,200 daily treatment fractions, providing a comprehensive assessment of positioning reproducibility in routine clinical practice. Because multiple fractions originated from each patient, however, within-patient correlation was not modeled using repeated-measures approaches such as mixed-effects models; this limitation should be considered when interpreting the statistical findings. Second, all patients were treated with a single delivery technique (helical TomoTherapy) under MVCT-based image guidance, so the findings may not be directly transferable to other treatment units or image-guidance systems. The current statistical analysis focused on paired comparisons of setup shift values; therefore, dedicated agreement methods such as Bland-Altman analysis and intraclass correlation coefficients were not performed. These approaches could provide complementary information on systematic bias, limits of agreement, and interobserver consistency in future studies. Finally, the dosimetric consequences of the observed set-up variations were not quantified. Future prospective, multicenter studies would help confirm and extend these findings.

Conclusion

This study emphasizes the critical importance of accurate patient positioning in adjuvant BC RT to ensure effective treatment delivery and minimize risks to healthy tissues. Comparisons between the TomoTherapy automatic alignment system, RTTs, and physicians revealed high consistency in set-up shift measurements, with differences remaining within clinically acceptable margins. In addition, the findings demonstrated that the number of RTTs involved in the treatment process did not significantly impact measurement accuracy, and neither CTV nor boost volumes influenced positioning accuracy. Advanced imaging techniques such as MVCT effectively addressed volumetric and positional changes, maintaining alignment precision throughout the treatment process. These results underscore the value of integrating advanced technologies and rigorous protocols to optimize RT outcomes for BC patients.

Ethics Committee Approval: This study was approved by The Institutional Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (Approval No. 2025/010.99/16/17; May 27, 2025).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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