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Original Article

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Setup Error and Effectiveness of Weekly Image-Guided Radiation Therapy of TomoDirect for Early Breast Cancer

Mi Joo Chung, MD[1]
Guk Jin Lee, MD[2]
Young Jin Suh, MD[3]
Hyo Chun Lee, MD[1]
Sea-Won Lee, MD[1]
Songmi Jeong, MD[1]
Jeong Won Lee, MD[4]
Sung Hwan Kim, MD[1]
Dae Gyu Kang, MS[1]
Jong Hoon Lee, MD[1]

[1]*Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul,* [2]*Department of Internal Medicine, Seoul, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul,* [3]*Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul,* [4]*Department of Radiation Oncology, Kyungpook National University, Daegu, Korea*

Correspondence: Jong Hoon Lee, MD
Department of Radiation Oncology,
St. Vincent's Hospital, College of Medicine,
The Catholic University of Korea,
93 Jungbu-daero, Paldal-gu, Suwon 16247,
Korea
Tel: 82-31-249-8440
Fax: 82-31-242-3734
E-mail: koppul@catholic.ac.kr

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Purpose

This study investigated setup error and effectiveness of weekly image-guided radiotherapy (IGRT) of TomoDirect for early breast cancer.

Materials and Methods

One hundred and fifty-one breasts of 147 consecutive patients who underwent breast conserving surgery followed by whole breast irradiation using TomoDirect in 2012 and 2013 were evaluated. All patients received weekly IGRT. The weekly setup errors from simulation to each treatment in reference to chest wall and surgical clips were measured. Random, systemic, and 3-dimensional setup errors were assessed. Extensive setup error was defined as 5 mm above the margin in any directions.

Results

All mean errors were within 3 mm of all directions. The mean angle of gantry shifts was 0.6°. The mean value of absolute 3-dimensional setup error was 4.67 mm. In multivariate analysis, breast size (odds ratio, 2.82; 95% confidence interval, 1.00 to 7.90) was a significant factor for extensive error. The largest significant deviation of setup error was observed in the first week of radiotherapy ($p < 0.001$) and the deviations gradually decreased with time. The deviation of setup error was 5.68 mm in the first week and within 5 mm after the second week.

Conclusion

In this study, there was a significant association between breast size and significant setup error in breast cancer patients who received TomoDirect. The largest deviation occurred in the first week of treatment. Therefore, patients with large breasts should be closely observed on every fraction and fastidious attention is required in the first fraction of IGRT.

Key words
Breast neoplasms, Radiation, Radiotherapy setup error, TomoDirect

Introduction

Numerous randomized trials have clearly confirmed breast conserving surgery (BCS) followed by radiation therapy (RT) as a treatment modality comparable to mastectomy for early breast cancer. Thus, BCS plus RT is widely accepted as standard therapy in patients with early breast cancer [1-3].

Parallel-opposed tangential beams are the traditional RT technique for breast irradiation, covering the breast and chest wall. The lateral borders of the tangential fields are extended by 1-2 cm from the body surface to accommodate the setup errors and respiratory motion. Intensity-modulated radiation therapy (IMRT) is currently popular in clinical use due to improved conformity of breast targets, decreasing radiation dose to normal structures, and better outcomes than conventional techniques with regard to skin toxicity and cosmesis [4-7]. IMRT using simultaneous integrated boost is able to reduce the number of fraction and overall treatment time.

Considering these IMRT advantages, TomoDirect could be a suitable radiation modality for whole breast irradiation without nodal irradiation [8]. TomoDirect is a non-rotational treatment option of the TomoTherapy Hi-Art System (Accuray, Sunnyvale, CA) allowing for RT planning and delivery with a series of highly modulated linear beam paths [9]. The couch is moved along the cranial-caudal axis past the fixed fan beam path during delivery of each field. Beam intensity is modulated by the binary collimator. TomoDirect also can enable image-guided radiation therapy (IGRT) using a megavoltage computed tomography (CT) scan just prior to radiation treatment and verify the setup error before RT. This technique makes it possible to correct setup error by using IGRT, reducing treatment error. This study analyzes patient setup error in TomoDirect treatment and assesses risk factors associated with extensive setup errors. Additionally, we investigated effectiveness of weekly IGRT.

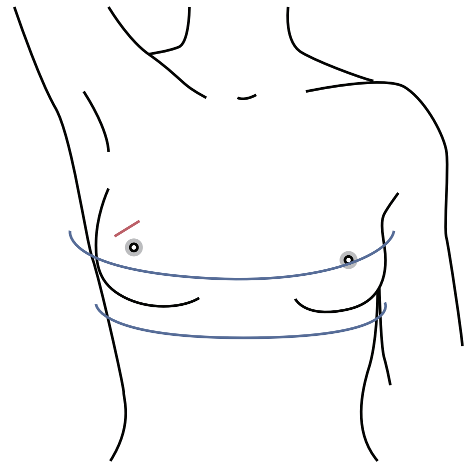

Fig. 1. A breast cancer patient was estimated their bust and underbust size with a measuring tape. The breast size was assessed by subtracting underbust size from bust size; small breast, bust size: underbust size < 10 cm; large breast, bust size: underbust size ≥ 10 cm.

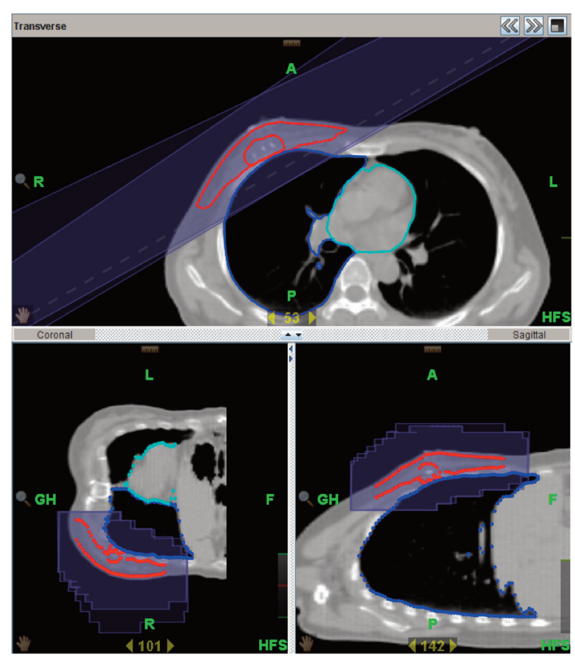

Fig. 2. TomoDiret planning images which deliver static beams in parallel-opposed angles.

Materials and Methods

1. Patients

One hundred and fifty-one breasts of 147 consecutive patients who underwent whole breast irradiation with TomoDirect after BCS for early breast cancer in 2012 and 2013 were evaluated. We reviewed all medical records including radiology, pathology, operation, and radiation. Institutional Review Board approval was obtained prior to chart review. Eligibility criteria were as follows: (1) histologically proven invasive breast cancer; (2) pTis or pT1-2 with node-negative stage according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system. Exclusion criteria were pT3-4 or pN+. RT was delivered immediately after BCS or sequentially after BCS followed by adjuvant chemotherapy. All patients were measured for their bust and underbust circumference on simulation day (Fig. 1). The breast size was classified into two categories. When the difference between the bust and underbust circumference is below 10 cm, the breast is defined as small. A difference over 10 cm is defined as a large breast [10].

2. Simulation, target definition, and dose prescription

The simulation was done in a supine position. All patients were immobilized with wing boards with both arms raised. Patients underwent CT scans for 3 mm-slice thickness from

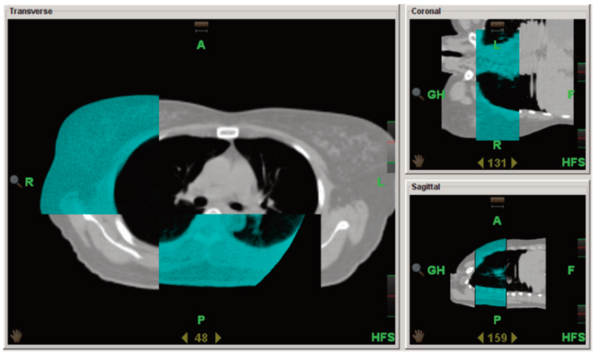

Fig. 3. Transverse, coronal and sagittal images show the extensive setup error (> 5 mm) in a breast cancer patient with a large breast by comparing simulation and megavoltage computed tomography before radiation therapy.

the lower neck to the mid abdomen. Reference points were marked on the skin on the anterior chest and bilateral intercostal surfaces. According to the contouring guideline, the whole breast planning target volume (PTV) included breast palpable tissue and the tumor bed [11,12]. Two tangential beams with a jaw width of 2.5 cm were used. Beam angles were selected to minimize dose to normal tissues and avoid irradiation to the contralateral breast (Fig. 2). A total of 50.4 Gy and 57.4 Gy in 28 fractions were prescribed to the whole breast PTV and tumor bed, respectively.

Table 1. Patient characteristics (n=151)

Characteristic	Value
Age (yr)	50 (25-83)
Body mass index (kg/m^2)	24 (16-33.8)
Site	
Right	77 (51)
Left	74 (49)
T stage	
pTis	49 (32.5)
T1	87 (57.6)
T2	15 (9.9)
Tumor location	
Upper	124 (82.1)
Lower	27 (17.9)
Axillary staging	
None	46 (30.5)
Sentinal node biopsy	12 (7.9)
Axillary node dissection	93 (61.6)
Lymph node dissected	9 (0-31)
≤ 12	98 (64.9)
> 12	53 (35.1)
Presence of seroma ≥ 15 mL	
No	125 (82.8)
Yes	26 (17.2)
Breast size	
Small	117 (77.5)
Medium to large	34 (22.5)
Adjuvant chemotherapy	
No	95 (62.9)
Yes	56 (37.1)

Values are presented as median (range) or number (%).

3. Verification

We performed weekly IGRT. The contour of PTV and lung were transmitted to digitally reconstructed images, from virtual simulation. For the setup process of radiation treatment, all patients were verified through coincidence between skin center and room laser. Before treatment, we acquired megavoltage CT (MVCT) image with a minimum of 5 cm above and below the level of PTV in the treatment position.

The first MVCT images were carried out and merged automatically into the kilovoltage CT treatment planning images, and the anterior-posterior, right-left, superior-inferior, and angle of gantry shifts (i.e., table angle correction for patient's trunk rotation during IGRT) were calculated by automatic image fusion for soft tissue matching. After automatic breast tissue matching between simulation CT and MVCT, the scanned images were manually adjusted for the chest wall and surgical clip. The setup errors were verified by one clinician and one radiation therapist.

In this study, systemic error (∑) was defined as the deviation of the geometry between fractionated treatment and simulation isocenter. Random error (σ) was defined as the deviation that occurred by fraction-to fraction errors [13]. In the study, extensive setup error was defined as 5 mm above margin along any directions (Fig. 3) [13]. Breast seroma of ≥ 15 observed in simulation CT scan was considered statistically significant [14].

4. Statistical analysis

A chi-square test was used to evaluate the univariate significance of the association between setup uncertainty and several clinical factors including breast size, body mass index (BMI), status of seroma, and extent of axillary lymph node sampling. Multivariate analysis was done by logistic regression. The flow of setup error was analyzed by repeated measure analysis of variance. Null hypotheses of no difference were rejected if p-values were less than 0.05, or, equivalently, if the 95% confidence intervals of risk point estimates excluded 1.

Table 2. Measurement of set-up error using megavoltage computed tomography scan

Error	Right to left (mm)	Superior to inferior (mm)	Anterior to posterior (mm)	3-dimensional (mm)	Angle of gantry (°)
Systemic	1.98±0.86	2.02±1.01	2.99±1.20	4.67±1.28	0.60±0.25
Random	1.87±0.88	2.10±1.04	2.82±1.64	2.06±1.07	0.54±0.31

Values are presented as mean±standard deviation.

Table 3. Univariate and multivariate analysis of factors affecting extensive set-up error

Factor	No. (%)	Univariate p-value	Adjusted OR (95% CI)	Multivariate p-value
Age (yr)		0.087		0.675
≤ 50	78 (51.7)		1.00 (reference)	
> 50	73 (48.3)		1.18 (0.54-2.50)	
Body mass index (kg/m^2)		0.143		0.716
≤ 24	77 (51)		1.00 (reference)	
> 24	74 (49)		0.86 (0.39-1.90)	
Breast size		0.022		0.049
Small	117 (77.5)		1.00 (reference)	
Medium and large	34 (22.5)		2.82 (1.50-7.90)	
Chemotherapy		0.083		0.172
No	95 (62.9)		1.00 (reference)	
Yes	56 (37.1)		1.80 (0.77-4.10)	
Site		0.078		0.128
Right	77 (51)		1.00 (reference)	
Left	74 (49)		1.77 (0.84-3.70)	
Tumor location		0.074		0.341
Upper	124 (82.1)		1.00 (reference)	
Lower	27 (17.9)		0.68 (0.31-1.40)	
Node dissected		0.051		0.189
≤ 12	98 (64.9)		1.00 (reference)	
> 12	53 (35.1)		0.6 (0.28-1.20)	
Presence of seroma ≥ 15 mL		0.053		0.110
No	125 (82.8)		1.00 (reference)	
Yes	26 (17.2)		2.53 (0.80-7.90)	

OR, odds ratio; CI, confidence interval.

Results

One hundred and fifty-one breasts of 147 consecutive patients were included in this study. Baseline characteristics are summarized in Table 1. The median age was 50 years (range, 25 to 83 years) and median BMI was 24 (range, 16.0 to 33.8 years). There were 77 (51%) right breast lesions and 74 (49%) left breast lesions. Forty-nine patients (32.5%) enrolled were diagnosed with ductal or lobular carcinoma *in situ*. Eighty-seven (57.6%) had T1 tumors and 15 (9.9%) had T2 tumors. One hundred twenty-four lesions (82.1%) were discovered in upper quadrants and 27 lesions (17.9%) in lower quadrants. Ninety-three patients (61.6%) underwent axillary lymph node dissection, and 12 patients (7.9%) had sentinel lymph node biopsy. Significant seroma of ≥ 15 mL were observed in 26 patients (17.2%) in simulation CT scan. One hundred seventeen patients (77.5%) had small breast size. Fifty-six patients (37.1%) underwent adjuvant chemotherapy.

Table 2 shows setup uncertainties of whole breast irradiation using MVCT. The mean systemic anterior-posterior error was 1.98 mm, right-left was 2.02, and superior-inferior 2.99. The mean random anterior-posterior error was 1.87

Table 4. Variation of weekly absolute 3-dimensional distance of setup errors during breast irradiation using TomoDirect

Setup error	Week				
	1	2	3	4	5
Absolute 3-dimensional error (mm)	5.68±2.99	4.53±1.99	4.35±2.11	4.31±1.97	3.93±1.83

Values are presented as mean±standard deviation.

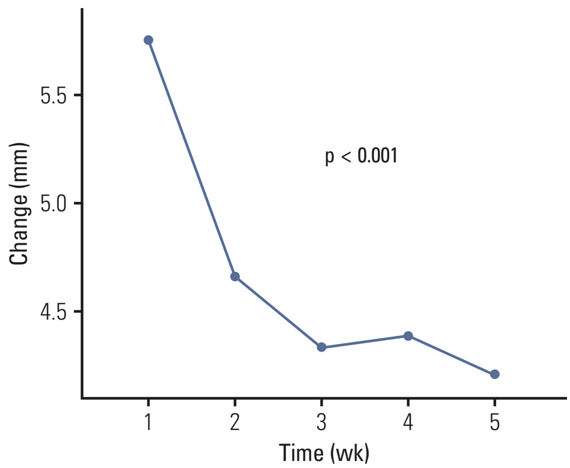

Fig. 4. Change of weekly absolute 3-dimensional distance of set-up error in whole breast irradiation using TomoDirect.

mm, right-left 2.10, and superior-inferior errors 2.82. All mean systemic and random errors toward any direction were within 3 mm. The mean angle of gantry shifts was 0.6°. The mean 3-dimensional distance of systemic setup error was 4.67 mm, and random setup error was 2.06 mm. The univariate and multivariate analyses of extensive setup errors are summarized in Table 3. In the univariate analysis, breast size ($p=0.022$) was significantly associated with extensive setup error. However, BMI, chemotherapy, tumor location, number of dissected lymph nodes, and seroma status were not associated with extensive setup error. Additional multivariate logistic regression analysis showed that breast size (odds ratio, 2.82; 95% confidence interval, 1.00 to 7.90; $p=0.049$) was significantly associated with extensive setup error. Fig. 4 shows the change of weekly absolute 3-dimensional distance of setup errors. The flow of error was analyzed by repeated measure ANOVA. The change of weekly mean absolute 3-dimensional distance of setup errors during breast irradiation using TomoDirect is summarized in Table 4. The significant biggest change of setup deviation was observed in first week and weekly setup errors decreased gradually over time ($p < 0.001$). The mean value of absolute 3-dimensional distance of setup error was 5.68 mm in the first week, and the mean width of change was within 5 mm after the second week.

Discussion

This study assessed the setup error in early breast cancer using TomoDirect with weekly IGRT. The average setup errors measured were within the 3 mm of anterior-posterior, right-left, and superior-inferior directions, 0.6° of gantry angle shift, and < 5 mm of absolute 3-dimensional distance. Our study suggested that PTV margins from tumor bed target volume of 6 mm along all directions was adequate to cover setup error. The most significant setup error was observed in the first week despite the coincidence between the skin center and room laser. The error was gradually reduced with careful setup process. Patients tend to get nervous on their first radiotherapy, and the resultant muscle tension and irregular respiration could contribute to the large setup errors [15]. In addition, the radiation therapist is not used to the setup of an individual patient during the first week of breast radiation. The setup errors reflect the course of patient's adaptation to the environmental change during the first week. Thus, radiation oncologists need to educate the patients for simulation and treatment process and deliver concrete setup information for breast size, respiration, arm position, and edema to the radiation therapists to minimize patient setup errors in the first week.

Breast size (the difference between bust and underbust) had a large effect on setup error. Hence it is recommended that meticulous caution should be paid to large-breast patients on every fraction. Other patient characteristics, including age, BMI, number of dissected lymph node, or presence of seroma, were not associated with extensive setup error in this study. In our previous study, a volumetric change of the tumor bed cavity was frequent. Patients with seroma after surgery had a significant volume reduction of 5% or greater in the tumor bed during conventional breast irradiation [16]. Accordingly, we anticipated that seroma was significant in volumetric change, but the presence of seroma had a marginal effect on setup error in this study.

Several studies analyzed the setup error with cone-beam CT (CBCT) or electronic portal image devices (EPID) for breast cancer. Lirette et al. [17] performed a prospective study to assess the precision and the reproducibility of the tangential breast irradiation technique with the help of on-line EPID. This study demonstrated that day-to-day variations in tangential breast treatment setup were acceptable and within the 5-mm recognized acceptable limit. EPID has many advantages in the ability to detect patient positioning setup deviations. Topolnjak et al. [18] treated 20 breast cancer patients to quantify the differences in setup errors measured with the CBCT and EPID. EPID registration underestimated the actual bony anatomy setup error in breast cancer patients by 20% to 50%, but using CBCT decreased setup uncertainties significantly.

Yang et al. [14] treated 176 consecutive breasts in 174 patients. Electronic portal image from 914 medial and 807 lateral directions were reviewed. Tumors in the upper outer quadrant, chest wall thickness ≥ 2.0 cm for medial portals, and age over 40 for lateral portals were associated with extensive errors. In our study, we observed the most significant setup error in the first week. Yang et al. reported that extensive error on the initial fraction had a high probability of extensive setup errors in both portals. In our analysis, the mean systemic anterior-posterior error was 1.98 mm, right-left was 2.02, and superior-inferior errors was 2.99 mm. All mean errors were within 3 mm of all directions. The absolute 3-dimensional distance of setup error was about 5 mm. In accord with our results, Offerman et al. [19] in their evaluation of setup errors using helical TomoTherapy, suggested that the mean random shift for all patients in the lateral direction was 2.7 mm, longitudinal was 3.1, and vertical 3.2 mm. The mean absolute distance shifted was 6.0 mm. Our results of setup errors were very similar to this published study.

Our results should be interpreted with the caution that there was no breathing control in our analysis [20]. Respiratory movements during normal breathing may be ignored for conventional whole breast irradiation [21]. However, for IMRT, respiratory movements are a matter of concern. Respiratory movement can lead to significant setup error according to Bert et al. [22].

Conclusion

The setup error for early breast cancer patients who receive weekly IGRT using TomoDirect, are within 3 mm. Large breast size was significantly associated with extensive setup errors. The biggest deviation of setup errors was observed in the first fraction during breast irradiation. Thus, weekly IGRT using TomoDirect in early breast cancer could be acceptable. However, patients with large breast size should be closely observed at all times, especially in the first week of treatment.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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