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Original Article

Analysis of whole breast displacement relative to selected skin markers and surgical clips using four-dimensional computed tomography

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Abstract: Objective: To explore the relationship between the displacement of the whole breast target and the displacement of a selected skin marker, the nipple and a selected surgical clip using four-dimensional computed tomography (4DCT). Methods and materials: Thirteen breast cancer patients who had undergone breast-conserving surgery were recruited for whole breast intensity-modulated radiotherapy (IMRT), and respiration-synchronized 4DCT image data were gathered during free breathing. The correlation between the displacement of the whole breast and the displacement of the clip, nipple and skin marker were analyzed. The changes in ipsilateral lung volume were analyzed during the respiratory cycle relative to the displacement of the breast. Results: There was no significant difference between the volumes of the whole breast targets at the selected end-inspiration (EI) and end-expiration (EE) phases. No meaningful correlation established between the breast and lung volume variance with the target motion. According to a population-based analysis, the displacement of the whole breast target was only significantly associated with the displacement of the superior clip along the Y-axes ($r = 0.657$, $P = 0.015$). Conclusion: The changes in breast and lung volume cannot be used to identify the target displacement. The selected clip in the surgical cavity may serve as a useful surrogate for tracking whole breast target movement during radiotherapy.

Keywords: Breast-conserving treatment, target displacement, four-dimensional computed tomography, skin marker, surgical clip in cavity

Introduction

Following breast-conserving surgery, adjuvant whole-breast irradiation is the standard treatment for early breast cancer, because possible microscopic disease may remain after the gross tumor has been excised [1, 2]. Currently, intensity-modulated radiotherapy (IMRT) after breast-conserving surgery delivers a uniform dose to the target volume, while minimizing the dose to the underlying lung, heart and surrounding normal tissues. Many studies have shown that target movement during irradiation generates dosimetric variations in the target, and that intrafraction movement stems primarily from respiratory movement and is patient-specific [3, 4].

Respiratory motion causes anatomical movement and leads to decreased target coverage or/and decreased normal tissue sparing, resulting in an increased risk of treatment failure or complications, such as late cardiac mortality and radiation-induced pneumonitis [5]. A linear model was developed to compare the dosimetric coverage difference introduced by respiration to the motion information [6]. Using this model, the dosimetric coverage difference introduced by respiratory motion could be evaluated during patient CT simulation. Kinoshita *et al*. [2] reported that as long as the conventional wedge-pair technique and the proper immobilization are used, the intrafraction three-dimensional (3D) change in the breast surface did not significantly influence the dose distribution. A number of studies have reported that respiratory gating can also abate the effect of tumor mobility in radiotherapy for mammary cancer following breast-conserving surgery, thereby ensuring the precise delivery of radiation dose to the target and achieving a high dose conformity around the target while reducing the overall irradiated volume to reduce normal tissue complications [5].

Skin markers and surgical clips in the lumpectomy cavity are representative for position verification of the tumor bed, and they are also used for irradiation set-up alignment. The displacement of the surgical clip in the lumpectomy cavity and the margins extended from clinical target volume (CTV) to the planning target volume (PTV) can be acquired based on three-dimensional CT (3DCT) and cone beam CT (CBCT) [7-9], however, since they are 3D image-guided studies, they do not show the relationship between the respiratory cycle phases and the target displacement. In contrast, four-dimensional CT (4DCT), which is based on time-stamped CT images collected during the full respiratory cycle at each table position and is associated with fewer respiratory movement-associated artifacts, can provide variable spatial position information during normal respiration [10, 11]. The 4DCT approach provides more accurate target localization during the respiratory cycle and a more optimal determination of the patient-specific planning target volume [12, 13]. In the current study, we investigated the whole breast displacement induced by respiration during IMRT and the relationship between the displacement of the whole breast relative to the displacement of a selected skin marker, the nipple and a selected surgical clip using 4DCT scanning.

Materials and methods

Patient eligibility

Patients who participated in this study were deemed in need of receiving whole-breast IMRT. All of the patients who underwent lumpectomy and axillary lymph node dissection had surgical clips placed in the cavity. Patients with restricted arm movements after surgery and poor pulmonary function or preexisting respiratory problems were excluded. Written informed consent was obtained from all of the patients before they were enrolled in the study. The study was approved by the Research Ethics Board of the hospital.

Patient data

13 breast cancer patients who had undergone 4DCT simulation in the treatment position were enrolled in the current study. Patients who participated in this study were diagnosed with invasive ductal carcinoma of the breast. The median age of the participating patients was 46 years (range 34-54 years); nine of the patients had a left-sided breast tumor, and the remaining patients had a right-sided tumor; seven patients had Stage I disease, six patients had Stage II disease.

Immobilization and surface markers

Patients were immobilized in a supine position on a breast board using an arm support (with both arms raised above the head to expose the breast adequately) and a knee support. Alignment to the reference point (using lasers on both of the patient's sides at the end of the inhalation breathing phase) and three laser alignment lines were marked on the patient prior to the CT acquisition. At the treatment unit, the patient was positioned by aligning the marker with the laser-system.

4DCT data acquisition

4DCT data sets were acquired in axial cine mode on a 16-slice CT scanner (Philips Brilliance Bores CT, Netherlands) for each patient during FB. The respiratory signal was derived from the Real-Time Position Management (RPM) Respiratory Gating System (Varian Medical Systems, Palo Alto, CA). The cine CT images along with the RPM trace were reconstructed to produce CT images, and the images were reconstructed with a slice thickness of 2 mm. The standard RPM software identified the entire breathing cycle and then equally subdivided each respiratory cycle into 10 phases, labeled as 0-90%. Phase 0% nominally denoted the end inspiration (EI) phase, and phase 50% signified the end expiration (EE) phase. The 10 4D-CT image sets were exported to the Eclipse treatment planning system (Eclipse 8.6, Varian Medical Systems, Palo Alto, CA).

Target delineation

To eliminate interobserver variation, the same radiotherapist outlined the target on each of the 10 respiratory phases for each patient. The

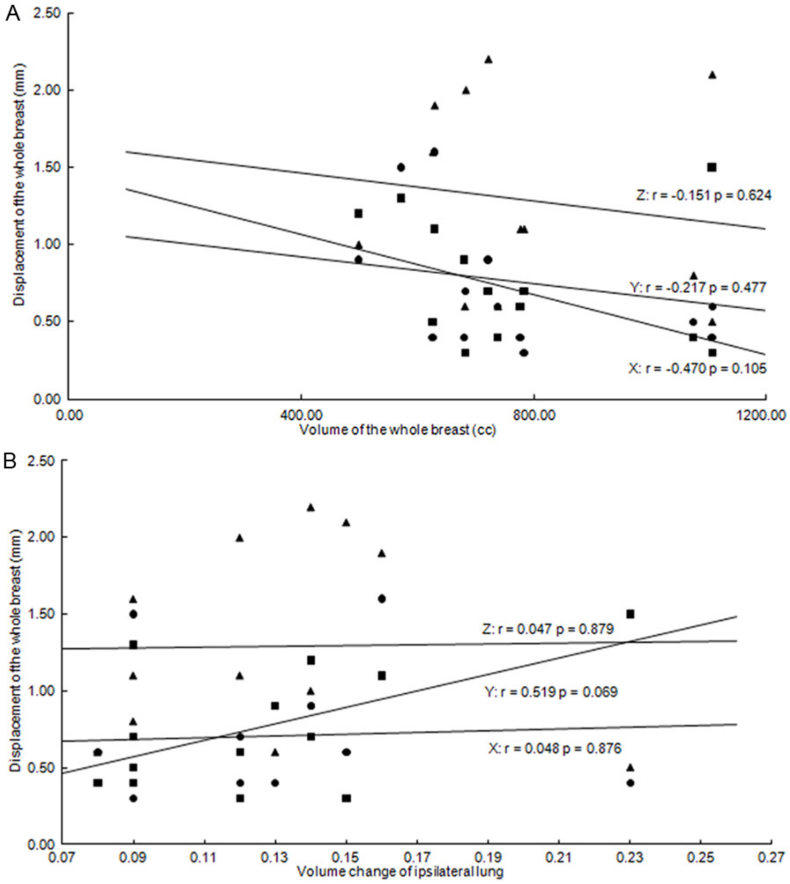

Figure 1. A. Whole breast displacement *vs*. whole breast volume in 4DCT scans. Circle, square and triangle represent the whole breast displacement in the mediolateral (X, ●), anteroposterior (Y, ■) and superoinferior (Z, ▲) directions, respectively. B. Whole breast displacement *vs*. ipsilateral lung volume in 4DCT scans. Circle, square and triangle represent whole breast displacement in the X(●), Y(■) and Z(▲) directions, respectively.

volume for each was contoured using the same window and level setting. All contouring was performed using Varian Eclipse software, which allowed for window/level adjustment, magnification and determination of the volume of the whole breast and ipsilateral lung, and the displacement of the center of the delineated targets (*i.e.*, the whole breast, nipple, superior clip and metallic skin marker) in the lateral (X), anteroposterior (Y), and superoinferior (Z) directions were achieved.

Statistical analyses

To assess the target motion, the geometric centers of the whole breast were calculated with software tools provided in the treatment planning system. Depending on the normality property of the data, Paired *t* tests were used to compare the displacement/volume values between the EI and EE phases. Pearson correlation was performed using the SPSS statistical analysis software package. The significance level was chosen to $\alpha = 0.05$.

Results

Patient characteristics

Patient compliance was high, and the patients easily understood the standardized breathing procedure. All 13 breast cancer patients who were recruited after breast-conserving surgery for whole breast IMRT underwent a simulation of big bore CT during FB, and 4DCT image data were gathered. Images were acquired using 4DCT for 11 patients with skin markers.

Respiratory motion range

The maximum displacement of the whole breast target in the FB state was 0.71 ± 0.42 mm (range 0.30-1.60 mm), 0.76 ± 0.40 mm (range 0.30-1.50 mm) and 1.29 ± 0.61 mm (range 0.50-2.20 mm) in X, Y and Z directions, respectively. Among these patients, the magnitude of the motion was typically the highest in the Z direction.

Relationship between the whole breast target and internal/external surrogate

Figure 1A showed a plot of the whole breast clinical target volume *vs*. the 3D displacement of whole breast for all 13 patients. There was no relationship between the 3D displacement of the breast and the whole breast target volume. The high degree of variation observed in the correlations between the volume change of the ipsilateral lung and the 3D displacement of the breast during the respiratory cycle indicated that there was no relationship between the

Table 1. Comparisons of the mean displacement and volume of the whole breast on two successive EI and three successive EE phases

Pt. no.	X (mm)		Y (mm)		Z (mm)		$V_{whole\ breast}$ (cc)	
	D_{EE}	D_{EI}	D_{EE}	D_{EI}	D_{EE}	D_{EI}	V_{EE}	V_{EI}
1	0.05	0.10	0.38	0.57	0.08	0.19	1106.81	1105.69
2	0.24	0.26	0.06	0.01	0.13	0.10	738.67	740.06
3	0.18	0.29	0.26	0.29	0.33	0.82	723.94	720.03
4	0.03	0.19	0.04	0.09	0.55	1.18	1,108.83	1100.59
5	0.04	0.12	0.02	0.13	0.14	0.11	1067.76	1082.48
6	0.25	0.13	0.03	0.18	0.65	0.27	627.31	635.77
7	0.08	0.17	0.09	0.14	0.33	0.50	685.99	678.96
8	0.01	0.01	0.15	0.15	0.31	0.51	625.13	624.61
9	0.05	0.03	0.21	0.22	0.15	0.40	784.85	783.12
10	0.39	0.24	0.45	0.33	0.33	0.09	570.52	571.51
11	0.15	0.08	0.21	0.27	0.15	0.07	777.12	778.13
12	0.12	0.18	0.32	0.36	0.28	0.49	498.96	498.54
13	0.02	0.02	0.34	0.38	0.20	0.27	673.98	685.79
Mean	0.12	0.14	0.20	0.24	0.27	0.38	768.45	769.63
SD	0.12	0.09	0.15	0.15	0.17	0.33	202.31	202.25
t Test	0.517		0.081		0.184		0.540	

Abbreviations: Pt. no. = patient number; X = mediolateral, Y = anteroposterior; Z = superoinferior; V_{EI} = volume of the two selected successive EI phases (90-0%), V_{EE} = volume of the three selected successive EE phases (40-60%); D_{EI} = mean displacement of the two selected successive EI phases (90-0%); D_{EE} = mean displacement of the three selected successive EE phases (40-60%); $V_{whole\ breast}$ = mean volume of the whole breast.

spatial displacement of the whole breast and the volume change of the ipsilateral lung (**Figure 1B**).

Table 1 provided comparisons of the displacement of the whole breast target between different respiratory phases in different 3D directions and also compared whole breast volume and ipsilateral lung volume in different respiratory phases. There was no significant difference between the mean target displacement in the different 3D directions and the selected two successive EI phases (90-0%) or the selected three successive EE phases (40-60%), and there was no significant difference between the volume of the breast at the selected EI and EE phases during the free breathing respiratory cycle.

In the X and Z directions, there was no relationship between the displacement of the breast and the displacement of the ipsilateral nipple, skin marker and superior clip in the cavity. In the Y-direction, the displacement of the whole breast target was only significantly related to the displacement of the superior clip (r = 0.657, *P* = 0.015) (**Figure 2**).

Discussion

Respiration contributes to the primary uncertainty of intrafraction motion of the breast during breast irradiation. Herein, we examined the centre of mass of the whole breast displacement using 4DCT, which was 0.71 mm, 0.76 mm and 1.29 mm in the X, Y and Z directions, respectively. Our results are similar to those reported in previous studies [2, 9, 14]. A study by Kinoshita *et al*. [2] of 17 breast cancer patients who received breast-conserving radiotherapy found that the range of the 3D intrafraction motion of the breast caused by respiration was 1.0 ± 0.6 mm, 1.3 ± 0.5 mm, and 2.6 ± 1.4 mm for the right-left, craniocaudal and anteroposterior directions, respectively. Kron *et al*. [15] evaluated breast movement using electronic portal cine imaging and found that the intrafraction motion associated with breast radiotherapy was much larger in the superoinferior direction (1.3 ± 0.4 mm) than in the mediolateral and anteroposterior directions. Taken together, results of the current study provide evidence that the movements of intrafraction targets caused by respiration during normal breathing are relatively small. But for different patients, the maximum variance of the target movement was 1.7 mm in Z axes, it is even more than the average displacement. Although we did not evaluate the interfraction displacement induced by setup error, based on these results, it should be possible to take individual margins to create the planning target volume into account.

In the current study, we concluded that the 3D displacement of the whole breast target did not correlate significantly with the volume of the whole breast during intrafraction irradiation (**Figure 1A**) in the FB state. This could be due to the fact that the breast were supported and filled with mammary gland lobules. Regardless

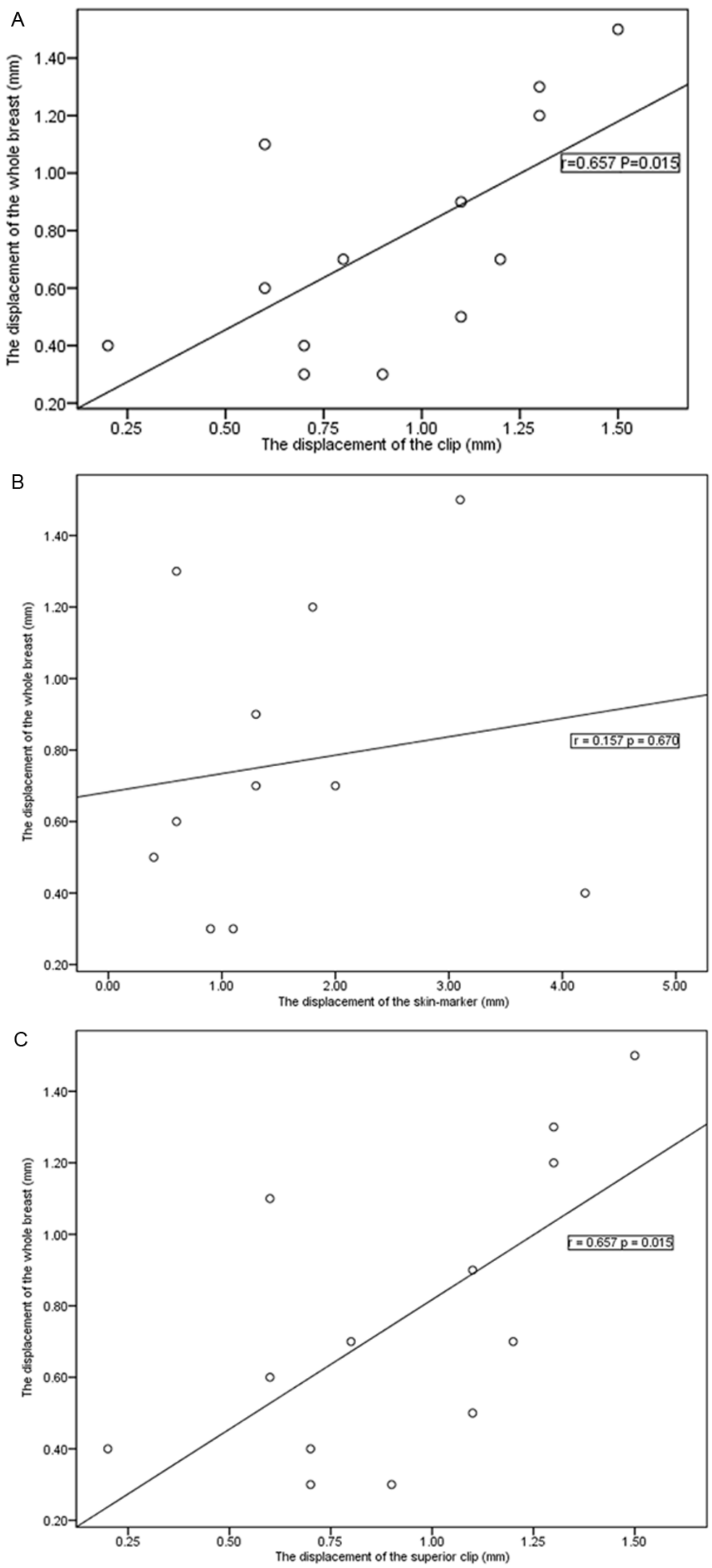

Figure 2. A. The displacement-relationship between the superior clip and the whole breast in the Y direction during free breathing. B. The displacement-relationship between the nipple and the whole breast in the Y direction during free breathing. C. The displacement-relationship between the skin marker and the whole breast in the Y direction during free breathing.

of the whole breast volume, during normal and free breathing, the filling of mammary gland lobules is used primarily to maintain the shape of the whole breast, rather than to directionally remodel the breast during intrafraction irradiation. The spatial position and movement of the breast induced by breathing did not agree well with the chest wall expansion to a certain extent during FB (**Figure 1B**).

The primary method that has been proposed to limit the magnitude of respiration-induced target motion during radiotherapy is breathing control. The chief breathing control approaches include active breathing control (ABC) and respiration gating (RG). Using the ABC system, Gagel *et al*. [14] showed a significant reduction of anatomic structure movement by monitoring and limiting respiratory volume. Borst *et al*. [16] reported that the mean and maximum doses of the deep inspiration breath hold (DIBH) treatment plan were significantly lower compared to the FB treatment plan for the organ at risk. Overall, however, at least for all of the patents in the current study, the intrafraction target displacement was limited and the influence of the intrafraction target displacement on the dose distribution was not significant during irradiation assisted by ABC.

However, the accuracy of ABC was affected by pulmonary function and the threshold of inspiration capacity that was chosen to perform ABC. RG ensures precise delivery of radiation doses to lesions that move during treatment. Korreman *et al*. [5] provided an overview of respiration-induced movement associated with breast irradiation, which showed that the mean excursions within the gating windows were lower than FB and ABC. Although several studies have clarified the relationship between the motion of surrogates and the tumor, and the appropriate phases to perform RGRT, these relationships and selected respiration-gated phases may differ for different types of cancer [17, 18].

For implementation of RG, the motion of the patient's respiration is monitored, typically by using a reflective marker and an infrared camera system. Because the target is generally not visualized, external and/or internal surrogates of tumor position are commonly used to trigger RGRT. Currently, two basic techniques are used to track target motion: internal fiducials and fluoroscopic imaging and indirect tumor monitoring with external markers and/or respiratory sensors [18-20]. In the current study, we investigated the correlation between the internal/external marker displacement obtained based on the 4DCT RPM and target movement for the whole breast. According to a population-based analysis, the present results show that the correlation coefficient for the Y direction motion between the internal fiducial implanted in the cavity and the whole breast was stronger (R = 0.657) than that between the target and external nipple and skin markers (R_{nipple} = 0.337, $R_{skin\ marker}$ = 0.145) on the series of 4DCT scans acquired under FB conditions. This finding indicated that the clip implanted in the cavity served as a good surrogate for verifying the whole breast target displacement during RGRT. Therefore, we can monitor the implanted clip to track the target movement during FB. These results provide evidence that the relative positions of the implanted surgical clips serve as a stable parameter for evaluating the displacement of the breast target during the course of radiotherapy treatment [21, 22].

Using 4DCT images, we quantified the displacement of the whole beast and the correlation of the breast with a selected skin marker, the nipple and a selected surgical clip. Respiration-induced whole breast displacement had a less correlation with the breast volume and ipsilateral lung volume variation. Furthermore, when compared with external markers, implanted surgical clips are more accurate and sensitive for verifying and correcting the position of the target during radiotherapy treatment.

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Disclosure of conflict of interest

None.

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