Residual Image Registration Error by Fiducial Markers in Accelerated Partial Breast Irradiation Using C-Arm Linac: A Phantom Study

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Abstract

Introduction: External beam accelerated partial breast irradiation (APBI) is an alternative treatment for patients with early-stage breast cancer. The efficacy of image-guided radiotherapy (IGRT) using fiducial markers, such as gold markers or surgical clips, has been demonstrated. However, the effects of respiratory motion during a single fraction have not been reported. This study aimed to evaluate the residual image registration error of fiducial marker-based IGRT by respiratory motion and propose a suitable treatment strategy.

Materials & Methods: We developed an acrylic phantom embedded with surgical clips to verify the registration error under moving conditions. The frequency of the phase difference in the respiratory cycle due to sequential acquisition was verified in a preliminary study. Fiducial marker-based IGRT was then performed in 10 scenarios. The residual registration error (RRE) was calculated on the basis of the differences in the coordinates of clips between the true position if not moved and the last position.

Results: The frequencies of the phase differences in 0.0–0.99, 1.0–1.99, 2.0–2.99, 3.0–3.99, and 4.0–5.0 mm were 23%, 24%, 22%, 20%, and 11%, respectively. When assuming a clinical case, the mean RREs for all directions were within 1.0 mm, even if respiratory motion of 5 mm existed in two axes.

Conclusions: For APBI with fiducial marker-based IGRT, the introduction of an image registration strategy that employs stepwise couch correction using at least three orthogonal images should be considered.

Introduction

Breast cancer is the most common cancer among women, with an estimated worldwide incidence of 2.2 million cases in 2020 [1]. Breast-conserving surgery followed by whole breast radiotherapy is the current standard of care for patients with early-stage breast cancer, and it is typically used to reduce the risk of local recurrence and increase overall survival [2, 3]. Several studies on the long-term efficacy of external beam accelerated partial breast irradiation (APBI) are currently being conducted and have demonstrated an outcome comparable to standard whole breast irradiation after breast conservation surgery [4–9]. To increase the dose homogeneity and conformity at the target and improve cosmesis, APBI with intensity-modulated radiation therapy or volumetric modulated arc therapy (VMAT) has been used in some clinical trials [8–10].

APBI requires more positional accuracy than whole breast irradiation as it involves delivering a high dose in hypofractions to a relatively small area. Image-guided radiotherapy (IGRT) ensures a highly accurate and precise patient positioning and consequently, efficient dose delivery. Several image-guided techniques have been applied to APBI treatment, including bone-based IGRT (e.g., chest wall and vertebral body), fiducial marker-based IGRT (e.g., gold markers or surgical clips) using megavoltage (MV) or kilovoltage (kV) imaging, 3D matching to the surgical cavity using cone-beam computed tomography (CT), and surface-guided radiation therapy (SGRT) [11–22]. Generally, these techniques exhibit higher positional accuracy than the traditional laser. Leonard et al. explored the feasibility of fiducial markers for

IGRT in APBI and determined that marker-based IGRT improved the setup accuracy by 2 or 3 mm [17]. Gierga et al. evaluated the performance of several setup methods, such as laser, bone anatomy, implanted clips, and SGRT, for APBI using the concept of target registration error (TRE) and reported a TRE of 2.4 mm for a clip-based setup [14]. Yue et al. reported that the marker-based approach can further improve the accuracy of the interfractional setup [21].

The role of fiducial markers in APBI treatment is two-fold: verifying breast position for IGRT as mentioned above and improving the delineation accuracy of the tumor bed as the surgical clips are directly sutured around the surgical cavity. Weed et al. reported that surgical clips serve well as strong surrogates of the lumpectomy cavity [23].

The point of concern for marker-based IGRT is that it may be sensitive to intrafractional motion caused by respiration, patients' subconscious motion, and other physiological movements. When imaging for a short time, such as kV or MV imaging, the boundary of the marker is clearly drawn and there may be no blurring due to motion. As a result, the markers appear in a different position for each image. Furthermore, with C-arm linac, the orthogonal images are acquired sequentially rather than simultaneously. Thus, there could be a phase difference in the respiratory cycle between anterior–posterior and lateral imaging. Although these are important considerations for a marker-based IGRT treatment strategy, previous studies have not evaluated the effects of respiratory motion during a single fraction. Therefore, the aim of this study was to evaluate the residual image registration error of fiducial marker-based IGRT by respiratory motion and to propose an appropriate treatment strategy.

Methods

Structure of the acrylic phantom with embedded surgical clips

Figure 1 shows the structure of the acrylic phantom with embedded surgical clips. We developed an original acrylic phantom (Taisei Medical, Osaka, Japan) that models surgical clips placed around the tumor bed in a patient with early breast cancer to verify the residual registration errors (RRE).

The size of the acrylic phantom was 10 cm × 10 cm × 10 cm, and crosshairs for reference were marked on all sides. A total of six 5.6-mm surgical titanium clips (Peters Surgical, Bobigny, France) were embedded in three dimensions. These clips were the same as those used for surgeries at our institution. The clips were randomly placed in a 3.5 cm × 3.0 cm × 3.0 cm area, assuming the four corners and the deep center of cavity, and the direction of the long axes of the clips were misaligned.

Influence of respiratory motion on CT simulation

CT simulation

We investigated the influence of respiratory motion during CT simulation on the delineation of clips and the clinical target volume (CTV) expansion from the clips. The acrylic phantom was mounted on a four-axis moving platform (4D-KAMUI, Anzai Medical, Tokyo, Japan), which comprised three orthogonal linear stages for the target (phantom) and a fourth stage for surrogate motion [24]. The crosshairs of the phantom were setup to match the laser in the CT room (i.e., the center of the image). The platform was powered using three computer-controlled, independent linear stages (45 mm/s maximum velocity; 1 mm maximum positional accuracy). The acrylic phantom was scanned in patterns for one static condition and three respiratory motion conditions using the SOMATOM Confidence RT Pro (Siemens Healthineers GmbH, Erlangen, Germany). CT scans were performed with no gating, e.g., breath-holding and four-dimensional CT. The sinusoidal waveform assumed for respiratory motion was employed, the motion patterns had an amplitude of 3 mm in the superior–inferior (SI) direction, 5 mm in the SI direction and 5 mm in the SI and anterior–posterior (AP) direction, respectively. The cycle was fixed at 4 seconds, and three sets of CT scans were performed for each condition to evaluate the influence between the scan timing and respiratory cycle. Reconstructed slice widths of 1 and 2 mm were selected to assess the slice width dependence on contours.

Delineation of the clips and CTV

The clips were manually delineated by a single medical physicist using a radiation treatment planning system (RayStation, version 9.0; RaySearch Laboratories, Stockholm, Sweden). The window/level and window/width were consistent for all CT images. The assumed CTV was expanded by adding 1.5 cm margins to each clip.

Influence of respiratory motion on orthogonal images of the linac

Phase difference in the respiratory cycle between images

In a preliminary study, we investigated the influence of respiratory motion on orthogonal images using an on-board imager (OBI) equipped on linac (Clinac iX, Varian Medical Systems, Palo Alto, CA, USA). The acrylic phantom and the four-axis moving platform were installed on the treatment couch in the same manner as the CT simulation. A total of 100 pairs of orthogonal images (kV sources, 0 and 270 degrees) were obtained under moving conditions, with patterns of sinusoidal waveforms with amplitudes of 3 and 5 mm in the SI direction (in this case, 200 pair images = 2 conditions × 100 images). The cycle was fixed at 4 seconds. There were no criteria in terms of beam-on start with respect to motion curve, and imaging occurred in a random manner. The displacement between the obtained orthogonal images and reference images was calculated. To eliminate any bias introduced by the difference between the CT and treatment rooms, orthogonal images with respect to the static condition were used as reference images. The phase differences of the SI direction were defined by the difference of longitudinal displacement between corresponding orthogonal images. An in-house MATLAB program (R2021a, The MathWorks, Inc., Natick, MA, USA) was developed to process the displacements caused by the respiratory motion.

Fiducial marker-based IGRT flow

Figure 2 shows the fiducial marker-based IGRT flow using OBI. Our proposed IGRT method employs a stepwise couch correction using at least three orthogonal images to infer the center of the clip under respiratory motion. In this study, orthogonal images were consistently and manually matched to the planned digital reconstructed radiography (DRR) based on each clip using the OBI software.

The following process was followed:

- (1) Register the first orthogonal images with the corresponding DRRs. Perform couch correction in the AP, SI, and left–right (LR) directions.
- (2) Register the second orthogonal images with the corresponding DRRs. If the need for a couch correction of >2 mm arises after registration, perform couch correction for half of the registration value in those directions; otherwise, do not perform couch correction.
- (3) Register the third orthogonal images with the corresponding DRRs. Perform couch correction based on the same criteria as in the previous step. If no couch correction is needed, complete the IGRT.
- (4) If couch correction was required in step (3), register the fourth images and perform couch correction based on the criteria used in step (2). Complete the IGRT with or without couch correction.

Note that the clips appear in a different position in each image because the orthogonal images are acquired sequentially rather than simultaneously. As a result, several factors must be taken into account for image registration. As there could be phase differences in the respiratory cycles between the AP and lateral images, image registration for the SI direction was performed for the middle position of the orthogonal images. For example, if the results from the registration were 3.0 and 1.0 mm in the AP and lateral directions, respectively, the final registration value would be 2.0 mm. Moreover, in theory, the phase differences will not exceed the respiratory amplitude. If there are phase differences close to the respiratory amplitude, their center position can be presumed to be the center of the mass of the clips. This can be applied to the registration between orthogonal images (e.g., AP vs. lateral images) and between images for the same gantry angle (e.g., AP image for the second vs. AP image for the third).

Evaluation of the RRE in fiducial marker-based IGRT

Figure 3 shows the method used to evaluate the RRE after three repeats of fiducial marker-based IGRT under respiratory conditions. The alphabets (a–e) in figures indicate the step of the procedure.

First, the crosshairs of the phantom mounted on the moving platform were set up to match the laser in the treatment room. Then, the phantom was moved to known arbitrary coordinates in the range of 0.5 cm to -0.5 cm (named Coord (X, Y, Z)₁), assuming a laser-based setup error in the clinical [(a) in Figure 3]. The coordinates X, Y, and Z indicate lateral, longitudinal, and vertical directions, respectively. Arbitrary coordinates were provided by the RAND function of Microsoft Excel, and these were blinded to the

therapists who performed image registration. The platform was run in a sinusoidal waveform with a 5-mm amplitude in the SI and AP directions, and fiducial marker-based IGRT flow was conducted as mentioned above [(b) in Figure 3]. After the last image registration, the acrylic phantom was stopped at the center of the amplitude and orthogonal images were acquired [kV0_last image and kV270_last image; (c) in Figure 3]. This verification was performed for different arbitrary coordinates of 10 scenarios.

The RRE, the distance between the center of mass of the clips (COMclip) on the reference images and that on the last kV orthogonal images were calculated to examine the positional accuracy of the center of the target using the in-house MATLAB program (Image Processing Toolbox™, rigid transformation algorithm) [(d) and (e) in Figure 3)]. The orthogonal images in the static condition were used as reference images.

For additional analysis, the RRE during the image registration process ($RRE_{REG1,2,3}$) was estimated by back-calculating from the final coordinates using the couch correction value. The RRE_{REG3} was calculated only when the fourth orthogonal image was taken.

Results

Influence of respiratory motion on CT simulation and structure delineation

The volumes of clips under static condition for the 1-mm and 2-mm slices were 0.35 and 0.41 cm³, respectively. During moving conditions, the change in clip volume showed no tendency to change with respect to the magnitude of amplitude and was 0.39 ± 0.03 cm³ for the 1-mm and 0.46 ± 0.03 cm³ for 2-mm slice. The structure volume of the 2-mm slice width showed a tendency to be larger than that of the 1-mm slice width. The clip volume for all moving conditions was larger than that of the static condition. In contrast, the clip+1.5 cm volume varied depending on the static and moving conditions. The clip+1.5 cm volumes under static conditions for the 1- and 2-mm slices were 78.6 and 81.6 cm³, respectively. During some parts of the moving conditions, the volume was smaller than that under the static condition. Figure 4 represents the relationship between clip volume and the clip+1.5 cm volume. The clip+1.5 cm volume increased as the clip volume increased.

Phase difference in the respiratory cycle between images

Figure 5 shows the fusion images for a reference static image (green) and the first moving image (magenta). The dotted lines were marked at the position of the superior and inferior clips of the reference images. The COMclip of kV 0 deg and kV 270 deg were acquired from -0.86 mm and 2.05 mm compared with the COMclip of the reference images. The phase difference in the respiratory cycle among the orthogonal images was 3.91 mm. Figure 6 presents a histogram summarizing all images for the acquisition position of each image and the phase difference between the orthogonal images. The acquisition positions of the clips were concentrated in a range of ± 2.0 –2.5 mm amplitude for both

images. As shown in Figure 6(b), the frequency seems to increase when the phase difference is small. However, the frequencies of the phase differences included in 0.0–0.99, 1.0–1.99, 2.0–2.99, 3.0–3.99, and 4.0–5.0 mm were 23%, 24%, 22%, 20%, and 11%, respectively, and relatively large phase differences (e.g., >2 mm) were noted with a probability of approximately 50%.

RRE in fiducial marker-based IGRT

Figure 7 shows the box plot of the RRE and those during the image registration process ($RRE_{REG1,2,3}$). The mean and standard deviation (SD) values are shown in Table 1. The magnitudes of the mean and SD (range) for the RRE for the SI, AP, and LR directions were 0.45 ± 0.42 (0.02–1.15) mm, 0.80 ± 0.72 (0.20–2.31) mm, and 0.51 ± 0.42 (0.09–1.05) mm, respectively. Five scenarios (Nos. 2, 5, 6, 9, and 10) required additional image registration (i.e., fourth image acquisition), and two of them (No. 5, 6) required couch corrections. The RRE reflects the results of the above corrections. The image registration error was smaller as the IGRT frequency increased, but the difference among the RRE and RRE_{REG3} , the result of the optional fourth IGRTs, and the usual three IGRTs was small. Figure 8 shows the coordinates of the COMclip for the last image and those of the COMclip if the phantom was stopped at the center of the amplitude. The coordinate of image 1 represents known arbitrary coordinates (Coord (X, Y, Z)₁). The end of the plot of the scenario where three (or four) set of images were taken is defined as “Image3 (or 4).” As mentioned above, the two scenarios required further couch correction using “Image4.” Although the target showed 5 mm of movement due to respiration, the RREs in the three axes converged using the proposed IGRT method.

Table 1
Residual registration error in fiducial marker-based IGRT for all scenarios

		SI	AP	LR
RRE	Mean $\pm$ SD	0.45 ± 0.42	0.80 ± 0.72	0.51 ± 0.42
	(Range)	(0.02–1.15)	(0.20–2.31)	(0.09–1.05)
RRE_{REG1}	Mean $\pm$ SD	1.03 ± 0.62	1.66 ± 0.71	0.67 ± 0.41
	(Range)	(0.02–2.06)	(0.49–2.51)	(0.09–1.09)
RRE_{REG2}	Mean $\pm$ SD	0.81 ± 0.47	1.16 ± 0.64	0.51 ± 0.42
	(Range)	(0.02–1.66)	(0.49–2.31)	(0.09–1.05)
RRE_{REG3}	Mean $\pm$ SD	0.51 ± 0.62	1.05 ± 0.43	0.51 ± 0.42
	(Range)	(0.02–1.93)	(0.20–2.31)	(0.09–1.05)
Abbreviations: SI, superior–inferior; AP, anterior–posterior; LR, left–right; SD, standard deviation; reg., registration; RRE, residual registration error.				

Discussion

In this study, we evaluated the influence of respiratory motion during CT simulation on the structural delineation of surgical clips. On the basis of the results of the preliminary study examining the influence of respiratory motion on orthogonal images using an OBI, we evaluated the RRE in fiducial marker-based IGRT under moving conditions.

The influence of respiratory motion on the delineation of the clips was negligible (maximum 30% in relative volume and 0.13 cm^3 in absolute volume) as the volume of the clip itself was exceedingly small. A larger volume was observed under the moving condition than with the static condition. The influence of a partial volume effect due to the slice width was also small. However, the clip+1.5 cm volume assuming CTV varied greatly based on the conditions of motion. This was due to the distance between the superior and inferior clips, which was wider (or shorter) because of the relation of respiratory motion and couch movement to the helical scan. This phenomenon occurred randomly, and it may be difficult to determine whether the clip distance is widened (or shortened) because it depends on respiratory amplitude and cycle as well as couch motion speed. In addition, because the clip was displayed at the wrong position on DRR, it may be impacted during image registration. Yue et al. reported that differences existed between the DRRs and the kV images in terms of geometrical position among the markers [21]. This may be caused by not only the volumetric change of the lumpectomy cavity after surgery but also the respiratory motion. Therefore, we recommend considering additional CT (e.g., four-dimensional CT or low-dose scan focusing on clips) in the clinical workflow to reduce the uncertainties. This additional information will enable the therapist to easily notice the difference in clip distances between planning the DRR and kV images in advance. This is not mentioned in previous reports, but it will be a key factor in fiducial marker-based IGRT.

Yue et al. reported that the phase difference uncertainty in the respiratory cycle between images is considered insignificant due to the fact that the respiration induced target movement is relatively small [21]. In previous studies examining respiratory motion of the breast, the mean $\pm$ SD of the respiratory motion in the LR, SI, and AP directions were $0.5 \pm 0.6 \text{ mm}$, $1.7 \pm 1.3 \text{ mm}$, and $2.3 \pm 1.8 \text{ mm}$ in the study by Yamauchi et al [10] and $1.0 \pm 0.6 \text{ mm}$, $1.3 \pm 0.5 \text{ mm}$, and $2.6 \pm 1.4 \text{ mm}$ in the study by Kinoshita et al [25]. The percentage of patients with a vertical amplitude of 3.1–5.0 mm and $>5.0 \text{ mm}$ was 8% and 12%, respectively [10]. Because the patients who exhibited amplitudes of 3 and 5 mm had a certain probability, we investigated the effect based on these amplitudes. In our preliminary study on the influence of respiratory motion on orthogonal images using OBI, the orthogonal images in which fiducial markers appeared in a different position by phase difference were observed frequently. The acquisition positions of the clips were concentrated in the amplitude range of ± 2.0 – 2.5 mm . This is the region where the speed changes in the sine waveform and the probability of a phantom per cycle is higher than any other region. Therefore, the larger the amplitude, the higher the probability of a phase difference. For clinical workflows, we suggest the necessity of a stepwise image guidance that takes into account phase differences, which is similar to the proposed method.

Fiducial marker-based IGRT was performed in accordance with clinical conditions using a clip phantom and a moving platform to verify the RREs. The mean RREs for all directions were within 1.0 mm, even if

there was a respiratory motion of 5 mm in two axes. However, as shown in Figure 7 and Table 1, there were differences with respect to the degree of convergence for RREs in the SI direction, which can be considered a phase difference of the orthogonal images, and the AP direction, which cannot be considered a phase difference. As image registration in the AP direction can only use lateral images, it must be noted that the image of a particular phase might be taken consecutively. To reduce the RRE for the AP (or LR) direction, it is necessary to not only use multiple images but also consider the positional relationship to organs such as the vertebral bone. Previous studies have demonstrated positional improvement using fiducial markers for APBI registration. Gierga et al. determined that the TRE for laser setup, bone anatomy alignment, clip-based alignment, and SGRT was 7.1 mm, 5.4 mm, 2.4 mm, and 3.2 mm, respectively [14]. Leonard et al. investigated the feasibility of fiducial markers for IGRT in APBI and proposed a reduction of the PTV margin from 10 mm to 5 mm [17]. Park et al. compared IGRT accuracy between bone and fiducial marker alignments and reported that fiducial marker-based IGRT allows a reduction of the PTV margin from 10 mm to 6 mm [18]. Yue et al. investigated respiratory-induced gold marker motion on kV imaging and found that intrafraction motion from respiration was 4.2 mm in magnitude. The interfraction errors from bone anatomy and laser setup were 7.1 mm and 9.0 mm, respectively [21].

Although it is not possible to make a general comparison because the subjects are different in the phantom and patients, our study showed a higher registration accuracy than that of previous studies that evaluated fiducial marker-based IGRT. The intrafractional motion due to respiration, baseline drift, and a patient's motion and physiological movements lead to uncertainty about the tumor bed position. The volumetric change in the lumpectomy cavity after surgery is a source of uncertainty throughout the treatment course. The RRE in patient studies increased because of these factors. Hoekstra et al. reported that the margin needed for intrafraction motion is highly dependent on the fraction duration, and the margin doubles to 2.0 mm for a fraction of 24 min compared with that of 8 min [26]. They recommend reducing the target drift by reducing the fraction duration. However, although using a less sophisticated IGRT protocol can save time, it may also lower the accuracy [26]. The mean duration (from the first to the last imaging) of the IGRT flow for 10 scenarios using the proposed method was approximately 7 min (range, 5–12 min). Although the RRE reduction effect of the fourth orthogonal images is limited, the RRE can be reduced to <2 mm in all axes using three stepwise IGRTs. Therefore, introducing the proposed image registration strategy can guarantee accuracy and save time. However, the validation of patient treatment is still limited and requires clarification in future studies.

Yamauchi et al. investigated the amplitude of the respiratory motion during VMAT-APBI delivery, which significantly affects dose distribution, and recommended considering respiratory motion management (e.g., breath-hold and shallow breathing) if the amplitude is >5 mm [10]. We believe that treatment during free breathing is reasonable and the feasibility of nongated IGRT during a single fraction was verified. Incorporating proper respiratory management with IGRT strategies can eliminate the concerns regarding fiducial marker-based IGRT.

Conclusion

We evaluated the influence of respiratory motion on CT imaging and found that the relative position difference between surgical clips depends on the timing of the affected scan and the expansion of the CTV. We observed numerous phase differences among the orthogonal images as the amplitude increased. Therefore, we recommend considering an image registration strategy that employs a stepwise couch correction using at least three repeats of orthogonal images. We reported our experience on fiducial marker-based IGRT using C-arm linac in a phantom study in which RREs was achieved at a clinically acceptable level.

Declarations

Conflict of interest: None

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Figures

Figure 1

Appearance of the acrylic phantom with embedded surgical clips

Figure 2

Fiducial marker-based image-guided radiotherapy flow using an on-board imager

Figure 3

Method to evaluate the residual registration error after three repeats of fiducial marker-based image-guided radiotherapy under respiratory condition

Figure 4

Relationship between clip volume and clip+1.5 cm volume. Abbreviations: SI, superior–inferior; AP, anterior–posterior

Figure 5

Fusion images for the reference static image (green) and moving image (magenta)

(a) Acquisition position

(b) Phase difference

Figure 6

Histogram showing (a) the acquisition position of each image and (b) the phase difference between orthogonal images

Figure 7

Box plot of the residual registration error (RRE) and the RREs during the image registration process ($RRE_{REG1,2,3}$)

(a) Superior-inferior

(b) Anterior-posterior

(c) Left-right

Figure 8

Coordinates of the center of mass of clips (COMclip) for the last image and those of the COMclip if the phantom was stopped at the center of the amplitude.