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ORIGINAL ARTICLE

# Inter- and intra-fraction geometric errors in daily image-guided radiotherapy of free-breathing breast cancer patients measured with continuous portal imaging

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## ABSTRACT

**Background.** Daily image-guided radiotherapy (IGRT) using two orthogonal setup images may be inaccurate for breast cancer patients treated in free breathing because the setup images may capture the patient in a breathing phase that is not representative of the mean anatomy. The aim of this study was to quantify the setup errors in breast radiotherapy after image-guided setup correction based on two orthogonal setup images acquired in free breathing.
**Methods and materials.** For 16 breast cancer patients with daily image-pair based IGRT, continuous portal imaging (7.5 Hz) were acquired at each treatment fraction during the delivery of the two tangential fields. For each portal image, the chest wall position relative to the planned position was determined in the imager direction orthogonal to the cranio-caudal direction. It yielded the time resolved setup error in this direction throughout the 16 treatment courses.
**Results.** The mean absolute setup error exceeded 5 mm in 0.9% (first field) and 1.8% (last field) of the treatments. The group mean error (M) and the standard deviations of the random ($\sigma$) and systematic ($\Sigma$) setup errors were $M = -0.7$ mm, $\Sigma = 1.1$ mm, $\sigma = 1.5$ mm (first field) and $M = -0.2$ mm, $\Sigma = 1.4$ mm, $\sigma = 1.7$ mm (last field). The negative sign of M indicates that less lung than planned was included in the treatment fields. Intra-field peak-to-peak chest wall motion amplitudes were patient dependent with patient mean values of $2.0 \pm 0.7$ mm [range 1.1–3.2 mm]. The largest observed intra-field motion amplitude was 8 mm.
**Conclusion.** Image-guided setup based on orthogonal planar images acquired in free breathing without synchronization with the respiratory phase was found to result in accurate tangential breast radiotherapy with only few outliers.

Patient setup errors may influence the treatment quality in radiation therapy of breast cancer patients [1]. Daily image-guided radiotherapy (IGRT) can reduce setup errors caused by day-to-day variations in patient positioning and thereby improve the treatment accuracy [2]. For breast cancer patients, daily IGRT based on non-ionizing imaging has been demonstrated with ultrasound imaging of the tumor bed [3] and optical imaging of the patient's surface [4,5]. X-ray-based IGRT is more common and uses either planar megavoltage (MV) [6] or kilovoltage (kV) [7] projection imaging to visualize contours of bony structures, lung, and patient surface, or cone beam computed tomography (CBCT) for full three-dimensional (3D) visualization of the patient anatomy [8]. While CBCT shows the patient anatomy averaged over several breathing cycles (the acquisition duration), the faster planar imaging techniques show a snapshot of the anatomy, typically captured in a random breathing phase that may not be representative for the mean anatomy.

The intra-fraction chest wall motion of breast cancer patients can be studied by continuous portal imaging acquired during treatment delivery [9–14]. Alternatively, the chest wall position can be monitored by magnetic sensors [15], or the surface motion can be measured optically [16] or with fluoroscopic x-ray imaging of a gold marker placed on the breast [17]. The advantages of continuous portal imaging include time-resolved visualization of internal motion during treatment delivery in the optimal view direction [beam's eye view (BEV) of the treatment beam]

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without additional imaging dose. Furthermore, no extra equipment is required, apart from an electronic portal imager device (EPID), and the geometrical setup error in BEV can easily be measured for conformal beams since the images show the anatomy relative to the field aperture. However, so far no study has used EPID to measure the geometrical errors during treatment of tangential breast fields after image-guided setup based on planar x-ray imaging. The setup imaging may capture the patient with a non-representative breast wall position leading to substantial setup errors after setup correction. Furthermore, continuous portal imaging has not previously been used throughout treatment courses to give a full time-resolved picture of the setup error at each treatment fraction. The current study evaluates the accuracy of daily image-pair based IGRT for breast cancer by continuous portal imaging at both tangential fields at all fractions in the treatment course.

## Material and methods

Sixteen breast cancer patients with a median age of 60 years (range 42–71 years) undergoing postoperative radiotherapy were included in the study. Eight patients had left-sided and eight patients had right-sided breast cancer. The patients were randomly selected among our patients in the daily clinic. Nine of the patients received whole breast radiotherapy (WBRT), whereas the remaining seven patients received locoregional radiotherapy after breast conserving surgery (n = 3) or mastectomy (n = 4).

The patients were positioned on a breast board (Candor ApS, Denmark) with the ipsilateral arm abducted 90–110° and CT scanned in free breathing for treatment planning. The patients were instructed to breathe normally both during the CT scan and during treatment. The treatment plans for WBRT patients used an isocentric technique with two 6 MV opposed tangential fields. For locoregional treatment, a three-field single isocentric technique was applied with two tangential 6 MV half-beam fields matched with an anterior half-beam field that was angled 12° from vertical for the axillary/supraclavicular region. For both plan types, a number of segments (typically 15 MV) were added to improve target dose homogeneity. Four of the WBRT patients were treated with 40 Gy in 15 fractions while the remaining 12 patients were treated with 50 Gy in 25 fractions, resulting in a total of 360 fractions.

The daily treatment procedure is summarized in Figure 1. First, at time t(MV) = 0, an MV portal image was acquired at the gantry angle of the first tangential treatment field, which was approximately 60° for right-sided (Figure 1) and 120° for left-sided breast cancer patients (not illustrated). Next, at time t(kV), an orthogonal kV image was acquired with the same gantry position using an On-Board Imager (Varian Medical Systems, Palo Alto, CA, USA). The setup images were registered manually with digitally reconstructed radiographs (DRRs) using the chest wall for the MV image and the anterior part of the ribs for the kV image. The resulting couch correction was calculated and performed automatically prior to treatment.

During delivery of the tangential treatment fields, continuous portal images were acquired with a PortalVision AS500 or AS1000 portal imager (Varian Medical Systems) with an imaging frequency of 7.5 Hz and pixel lengths when scaled to isocenter distance of 0.52 mm (AS500) or 0.26 mm (AS1000).

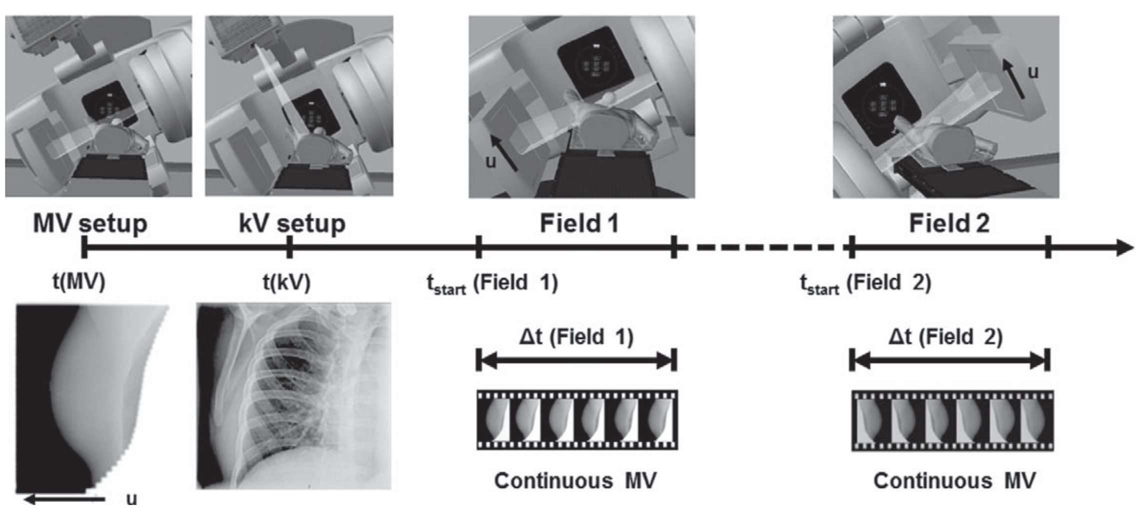


Figure 1. Daily setup procedure and imaging for a right-sided breast cancer patient. The MV and kV setup images were acquired at the same gantry angle (~60°).

The image acquisition and storage were carried out by the standard image management system used in the clinic (ARIA, Varian Medical Systems), however, with an imaging frequency considerably higher than for standard clinical use. The imaging was performed for both tangential fields at all 360 treatment fractions. As illustrated in Figure 1 the first tangential field (Field 1) was treated immediately after on-line couch correction at time $t_{start}$(Field1) relative to the MV setup image and had a treatment duration of $\Delta t$(Field1). The second tangential field (Field 2) was treated as the last field of the session at time $t_{start}$(Field2) with a duration of $\Delta t$(Field2). Additional segments and, for locoregional treatment, the field covering the supraclavicular/axillary region were treated between field 1 and field 2.

After the treatments, the portal images were exported as Dicom files from the image management system. An in-house built Matlab computer program was used for semi-automatic registration in all MV images of the chest wall position as well as the field edge in the u direction [i.e. in the direction in the imager plane that is perpendicular to the gantry rotation axis (Figure 1)]. The u direction is a linear combination of the left-right (LR) direction (approx. one third) and anterior-posterior (AP) direction (approx. two thirds) in patient coordinates. The registration resulted in the intra-treatment chest wall motion in BEV with an offset relative to the field edge that was arbitrary, but identical at all treatment fractions for a patient. The chest wall motion on an absolute scale, i.e. relative to the planned position within the field aperture, was obtained by manually registering the portal images with most extreme chest wall positions of one fraction for both fields with the corresponding DRR using the image analysis application in ARIA. It resulted in the absolute setup error in BEV for each portal image. From this, the mean setup error and peak-to-peak motion of the chest wall for each fraction were determined in the u direction for both tangential fields. Finally, the group mean error [M] and the standard deviation of the random ($\sigma$) and systematic ($\Sigma$) errors in the u direction were calculated for both tangential fields following van Herk et al. [18].

Besides error and motion analysis, the Matlab registration program was also used for temporal sorting of the portal images on a sub-second time scale, since the 7–8 images recorded within each second were unsorted due to identical time stamps in the image management system. The sorting was performed such that the breathing motion (i.e. the time resolved setup error) was a smooth semi-periodic function of time.

Statistics were carried out in Microsoft Excel version 2010 using two-sided Students t-test.

## Results

The timing of the imaging during treatment delivery is given in Table I. Images from 341 (Field 1) and 340 (Field 2) of the 360 fractions were available for analysis. For the remaining fractions, image analysis was not possible either because the EPID was positioned incorrectly in the longitudinal direction during image acquisition or because an excessive number of bad pixels in the EPID hindered reliable automatic chest wall registration. While all acquired images were correctly stored for field 1, the storage was occasionally incomplete for field 2 due to the non-standard high imaging frequency applied, meaning that the last recorded images were lost. Therefore, the average number of stored images per fraction was 70 for field 1 and only 61 for field 2.

Figure 2 shows the time resolved setup error over the complete 15 fraction treatment course for patient 1. Note the occasionally shorter length of recorded breathing motion for field 2 due to incomplete image storage. A negative deviation from planned position indicates that less lung than planned was included in the treatment fields. At some fractions, a large shift of the mean chest wall position occurred between field 1 and field 2. However, no systematic difference between the mean setup errors of fields 1 and 2 was observed ($p = 0.68$). An example of a large intra-fraction shift is shown in Figure 2 (fraction 2) suggesting that the patient lifted her back slightly during field 1 and had relaxed to nearly the setup position during field 2.

The distribution of mean setup errors for all fractions and patients is shown in Figure 3. No systematic difference between field 1 and field 2 setup errors was found ($p = 0.27$). Furthermore, no systematic difference between the mean setup error in the first five fractions and the last five fractions was observed ($p = 0.78$, field 1 and $p = 0.80$, field 2). Linear regression analysis showed a correlation between the mean setup error of field 1 and the corresponding error of field 2 ($r^2 = 0.66$, $p < 0.001$) (Figure 4). However, non-correlated deviations between the setup errors of the two fields were also occasionally observed (see, e.g. fraction 2 in Figure 2). Figure 5A presents a box plot of the patient-specific mean setup errors for

Table I. The timing during image-guided setup and treatment of the 16 patients.

| | Mean value (range) [min:s] |
|---|---|
| t(MV) | 0 |
| t(kV) | 0:56 (0:47–1:28) |
| $t_{start}$ (field 1) | 3:07 (2:16–4:55) |
| $\Delta t$ (field 1) | 0:11 (0:07–0:15) |
| $t_{start}$ (field 2) | 5:52 (4:12–8:36) |
| $\Delta t$ (field 2) | 0:11 (0:06–0:14) |

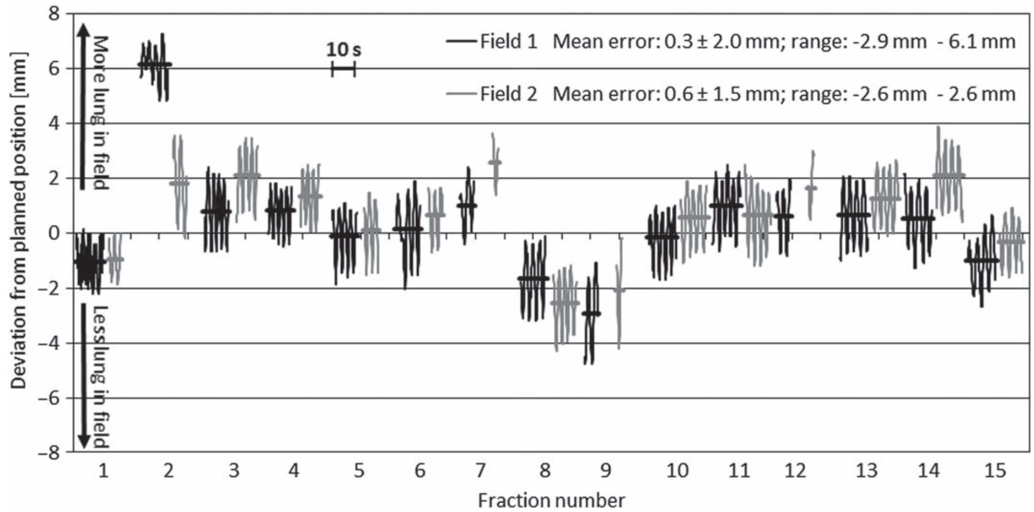


Figure 2. Time resolved setup error of the chest wall in the u direction over a complete treatment course for patient 1 who was treated with 40 Gy in 15 fractions. The horizontal lines show the field-specific mean setup error.

both fields. At three fractions, the absolute mean setup error exceeded 5 mm for both fields, indicating that setup imaging with the chest wall in a non-representative breathing phase occurred in 0.9% of the fractions. The absolute mean setup error was larger than 5 mm in additional three fractions for field 2 (Figure 3). Figure 5A illustrates that these occasional large setup errors were distributed over several patients: The three occurrences of large errors for field 1 were distributed over three different patients, and the six large errors for field 2 were distributed over five different patients. Group mean (M), random (σ) and systematic (Σ) setup errors were M = -0.7mm, Σ = 1.1mm, σ = 1.5mm, (field 1) and M = -0.2mm, Σ = 1.4mm, σ = 1.7mm (field 2). The negative sign of M indicates that less lung than planned was included in the treatment fields.

Figure 5B is a box plot the of peak-to-peak intra-field motion for each patient. The motion amplitudes were patient specific with mean values of 2.1 ± 0.7 mm [range 1.2–3.2 mm] (field 1) and 1.9 ± 0.7 mm [range 1.1–3.0 mm] (field 2). The largest peak-to-peak motion during delivery of a treatment field was 7.9 mm, observed for patient 15 due to a deep inspiration during the last part of field 2 in fraction 9. The peak-to-peak motion correlated only weakly with the daily absolute mean setup error (correlation coefficient 0.11). The intra-fraction motion variability, defined as the average intra-fraction standard deviation of the chest wall position [9,10], was 0.7 mm and 0.6 mm, respectively, when calculated with and without weighting with the patient-specific number of images (i.e. when calculated according to [9] and [10], respectively).

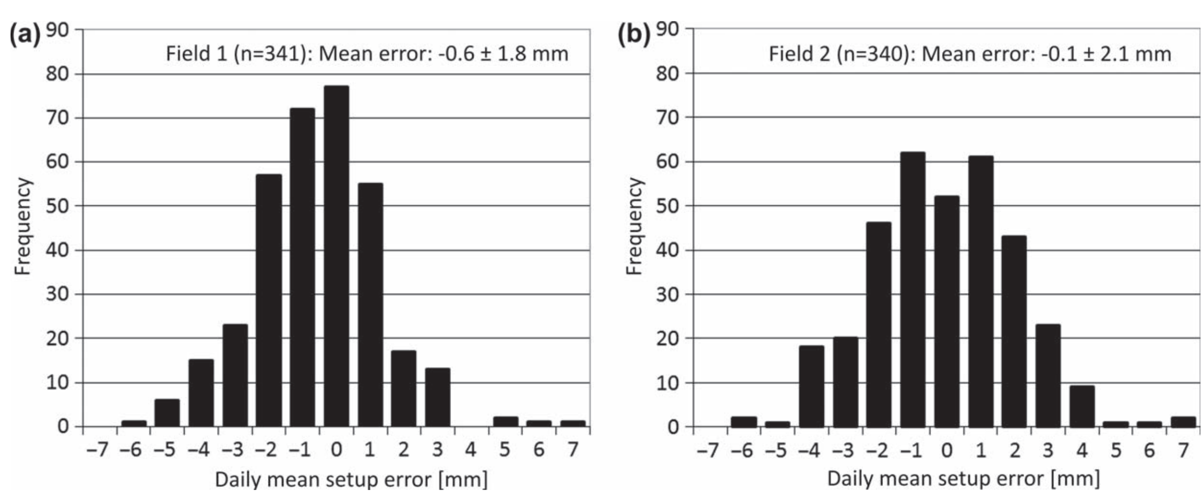


Figure 3. Distribution of daily mean setup errors in the u direction derived from continuous portal images for (a) field 1 and (b) field 2. A negative setup error means that less lung than planned was included in the field during treatment.

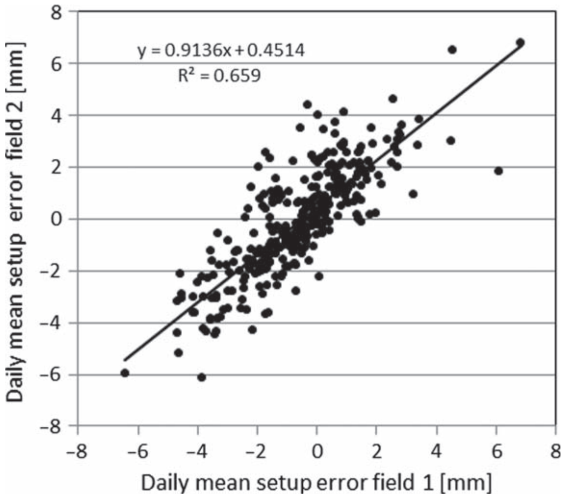


Figure 4. Scatter plot and linear regression analysis comparing the daily mean setup error of fields 1 and 2.

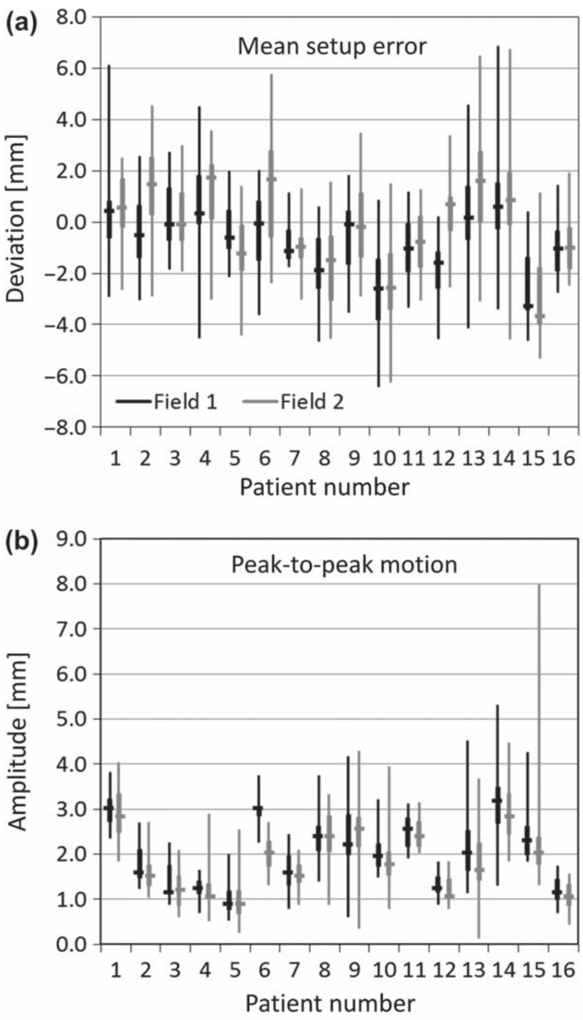


Figure 5. Box-plots showing for both tangential fields (a) the patient-specific mean setup error and (b) the patient-specific peak-to-peak intra-fraction motion in the u direction. The horizontal bars show the median of the mean setup error observed for each field during treatment delivery whereas the vertical bars represent the range with the lower and upper quartiles shown in a thin line.

## Discussion

For the first time, continuous portal imaging was used to determine the chest wall motion and time-resolved geometrical error after image-guided setup of breast cancer patients throughout complete treatment courses. Although continuous portal imaging has previously been used to study the intra- and inter-fraction chest wall motion during tangential breast treatments [9–12,14], the previous studies did not include pretreatment image-based setup corrections and they used less frequent imaging (maximum half of the treatment fractions) with lower imaging frequencies (0.3–2 Hz) compared with the 7.5 Hz imaging at each treatment fraction in the current study. The large day-to-day variations with occasional large setup errors (Figures 2 and 5A) show that daily continuous portal imaging has to be performed at each fraction to give the complete picture of the chest wall position during the treatment course. The high imaging frequency of 7.5 Hz gives more detailed mapping of the chest wall motion during complete breathing cycles with minimal blurring caused by residual motion during image exposure. Although beyond the scope of this study, the high imaging frequency gives sufficient time resolution for studying cardiac motion and unintentional cardiac exposure in left-sided treatments. Unlike previous continuous portal imaging studies [9–12,14], the current study quantifies not only the chest wall motion, but also the geometrical errors by comparison with the planned chest wall position within the field aperture in DRRs.

For the included 16 patients, no systematic shifts in chest wall position were observed during the treatment fractions (between field 1 and field 2) or during the treatment courses (from first to last fractions). Using optical surface scanning Gaisberger et al. [5] observed a systematic sag of their patients in a repeated scan performed approximately 2 minutes after the initial scan.

The standard deviations of systematic and random errors for the u direction, $\Sigma = 1.25$ mm and $\sigma = 1.6$ mm, were comparable to the values $\Sigma = 0.8$ mm and $\sigma = 1.8$ mm in the same direction derived from EPID images after online CBCT-based setup correction [8]. The acquisition of two orthogonal images is less time consuming and results in considerably less imaging dose than a CBCT scan [19]. Application of a standard margin recipe, $2.5\Sigma + 0.7\sigma$ [18] on the systematic and random errors in this study yields setup margins in BEV of 3.8 mm (field 1) and 4.7 mm (field 2), indicating that our institutional standard margin of 5 mm for breast cancer patients is sufficient.

The intra-fraction chest wall motion amplitudes of 1.1–3.2 mm are in accordance with Smith et al.

[11] and Richter et al. [12] who found patient dependent amplitudes in the range 2.0–2.5 mm and 0.8–2.2 mm, respectively, whereas the intra-fraction motion variability of 0.6–0.7 mm is only half of the variability found in [9] (1.6 mm) and [10] (1.1 mm). Our intra-fraction motion amplitudes were on average smaller than the amplitudes derived from high frequency kV imaging of a gold marker on the skin in [17]. Previous studies have also determined the inter-fraction motion. Kron et al. [10] defined inter-fraction variability as the standard deviation of the mean values on each day averaged over all treatment fractions and obtained a value of 1.8 mm. It corresponds to the standard deviations given in Figure 3, which were 1.8 mm (field 1) and 2.1 mm (field 2). Fein et al. [9] determined the inter-fractional variation by pooling of the individual patient standard deviations and obtained a value of 4.4 mm, which is nearly three times as large as the value 1.6 mm derived by using their formula on the data in this study. Finally, Smith et al. [11] found inter-fraction variations in the range 5.9–29.4 mm. However, the large differences between the two latter studies and this study may reflect the fact that daily IGRT setup correction was carried out in this study prior to treatment.

The use of continuous portal imaging for setup error assessment is limited to anatomy clearly visible inside conformal field apertures. A further limitation of the study was that it only included motion and geometrical errors in the u direction of the portal imager. For tangential breast fields, portal imaging is less accurate in estimation of cranio-caudal (CC) errors [8]. In the current treatments, the CC patient position is mainly determined by the orthogonal kV setup image. The main contribution to the setup errors after the IGRT procedure is expected to be respiratory motion, which is smaller in the CC direction than in the LR and AP directions (and thus the u direction) for breast cancer patients [20].

## Conclusion

Continuous portal imaging throughout entire treatment courses was used to determine the intra-treatment motion and setup errors for tangential fields of free-breathing breast cancer patients with daily image-pair-based IGRT setup. No systematic deviation in chest wall position between planning and treatment was observed. Intra-treatment motion of the chest wall was patient specific and in general quite small. Setup imaging with the chest wall in a non-representative breathing phase was observed in less than 1% of the treatment fractions. Thus, two sequential orthogonal planar images acquired in free breathing without synchronization with the respiratory phase can be applied safely for daily setup imaging in tangential breast radiotherapy.

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