Significant inter-fraction variations during tangential breast irradiation

An indication for image-guided radiotherapy for simultaneously integrated boost

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ABSTRACT

الأهداف: استخدام البيانات التي تم الحصول عليها من الصور الالكترونية المأخوذة أثناء العلاج الإشعاعي للثدي وذلك من أجل تقييم الاختلافات بين الجلسات، ومن ثم تحديد الهوامش المطلوب اعتبارها عند إعطاء الجرعة الإضافية في مكان الورم.

الطريقة: أُجريت هذه الدراسة الاستطلاعية الاستفتائية في مستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من فبراير إلى سبتمبر 2009م، حيث شملت 10 مريضات يخضعن للعلاج الإشعاعي لكامل الثدي بعد الجراحة التحفظية للثدي. لقد تم ترتيب وضعية المريضة إما باستخدام علامات الجلد أو علامات التشريح العظمية. وتم تصوير الحقل المماس الأنسي أثناء العلاج يومياً، وبعد ذلك تم حساب الإزاحة بين صور العلاج الالكترونية وصور التخطيط الرقمية المُعاد بناؤها. استخدمت الاختلافات بين الجلسات في تحديد الهوامش المطلوب اعتبارها حول مكان ورم الثدي وذلك عند إعطاء الجرعة الإضافية من العلاج.

النتائج: لقد لوحظ وجود اختلاف هندسي كبير في تحديد وضعية المريضة، وقد كانت الهوامش المطلوبة باستخدام علامات الجلد كالتالي: 15.6 ملم في الاتجاه الأمامي الخلفي، و15.4 ملم في الاتجاه القحفي العجزي، في حين كانت الهوامش المطلوبة عند استخدام العلامات العظمية كالتالي: 12 ملم في الاتجاه الأمامي الخلفي، و12.2 ملم في الاتجاه القحفي العجزي.

خاتمة: أثبتت الدراسة بأن وضعية المريضة أثناء العلاج الإشعاعي للثدي تحتوى على العديد من الاختلافات المنهجية والعشوائية مما يستدعى وجوب وضع هامش كبير عند إعطاء الجرعة الإضافية في مكان الورم. وهكذا تتضح أهمية استخدام تقنية العلاج الإشعاعي بمساعدة التصوير الالكتروني أثناء الجلسات العلاجية.

Objective: To use electronic portal images (EPI) to clinically evaluate inter-fraction variations during tangential breast irradiation, using either a skin marks setup, or a bony anatomy setup, and to determine the required margins for simultaneously integrated boost (SIB) planning target volume (PTV).

Methods: Ten patients undergoing radiotherapy to the entire breast with tangential fields, after breast conservation surgery were considered for this pilot prospective study in the Radiation Therapy Unit of King Abdulaziz University Hospital between February and September 2009. Patient setup was carried out either using skin marks or bony anatomy landmarks. The EPIs of the medial tangential radiation fields were performed daily; displacement of the EPI with respect to the digital reconstructed radiographs (DDRs) was quantified after manual registration with the corresponding DDRs and recorded in both antero-posterior (AP) and cranio-caudal (CC) directions. The inter-fraction variations were used to calculate required margins for SIB PTV.

Results: Considerable geometric uncertainties in patient positioning have been observed for both investigated treatment setup protocols. The margins required for a correct assessment of boost PTV were: 15.6 mm for AP and 15.4 mm for CC directions for the skin marks setup protocol, and 12 mm for AP and 12.2 mm for CC directions for the bony anatomy landmarks setup protocol.

Conclusion: Systematic and random errors induced by inter-fraction patient setup variations are significant in tangential breast radiotherapy, and lead to a large PTV margin for SIB. Such large margins indicate the need for image-guided radiotherapy.

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For patients with early stage breast cancer, breast radiation therapy is an integral component of breast-conserving therapy that has shown a local tumor control benefit and an overall survival benefit in several randomized trials.[1] Conventional breast radiation therapy is delivered to the whole breast with tangential breast fields, followed by a boost to the resection cavity,[2] to further improve local tumor control, as demonstrated in 2 randomized studies for invasive breast cancer,[3,4] and suggested in a retrospective analysis for ductal carcinoma in situ.[5] This sequential treatment technique is currently replaced in some centers by a simultaneously integrated boost (SIB) technique, which allows the delivery of a higher dose per fraction to the tumor bed compared to the whole breast.[6] With the SIB technique, the treatment duration compared to the conventional sequential treatment is reduced. Furthermore, it has potential advantages such as a more efficient dose delivery, a better biologic effectiveness, and a reduced dose delivery to normal tissues like lung and heart. Regardless of the technique used, breast boost irradiation raises issues of concern, as delineation uncertainties (for example, identifying the tumor bed after surgery, inter-observer variability in contouring the boost volume on CT images),[7-9] and position verification of the excision cavity.[10,11] The modern radiotherapy technology offers various methods for image-guided breast treatments, as kilo-voltage (kV) x-ray localization of surgically implanted clips, mega-voltage (MV) electronic portal imaging (EPI), optical. and video imaging. These methods use various surrogates as indicators for the position of the tumor bed.[12] In the particular case of MV EPI guidance, the common surrogate for the tumor bed is a bony landmark, mainly the chest wall. This assumption might not be accurate if the correspondence between the resection site and bony anatomy is poor. In the conventional tangential breast irradiation, where the target volume includes the whole breast, the setup error has been so far underestimated. The most commonly performed method of patient positioning for breast radiotherapy is based on skin-mark alignment to machine lasers and a visual verification of the correct light field coverage over the whole breast.[13] The chances of "missing" the target are therefore, small. With a SIB technique, however, the target volume of the boost is significantly smaller, and the probability of a geographical miss is consequently, higher. As radiotherapy treatments become more conformal, the image-guidance role becomes more important, to reduce the setup errors. The setup error determines the size of planning target volume (PTV) margins, therefore playing an important role in achieving dose objectives in the treatment planning process.[13] Patient setup for tangential whole breast radiotherapy can be verified with film or electronic portal imaging devices (EPIDs).[14-16] As these treatments employ nearly opposing fields, only 2-dimensional (2D) setup errors (namely, in the plane of the film or the EPID) can be determined and corrected. However, for a 3-dimensional conformal radiation therapy (3D-CRT) techniques, as SIB or accelerated partial breast irradiation (APBI), the setup verification and error correction should be considered, for adequate dose coverage in 3 dimensions. An inherent challenge of relying on bony landmarks as a surrogate for tumor bed is that the breast tissue is nonrigid and can move and deform with respect to the bony anatomy.[17]

The purpose of this study was to use data obtained from an EPID to clinically evaluate inter-fraction variations, using either a skin marks setup or a bony anatomy setup. The results of this study have implications for the accuracy of SIB or 3D-CRT techniques that will be used in the conservative radiation therapy of the breast, providing data for a correct assessment of boost PTV margins.

Methods. The biomedical ethics research committee of King Abdulaziz University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia approved this pilot prospective study. Ten consecutive patients undergoing radiation therapy after breast conservation surgery constituted the study group; the patients were treated in the Radiation Therapy Unit of KAUH between February and September 2009. Radiation therapy consisted of treatment to the entire breast with tangential fields; patients with either right or left breast undergoing treatment were included. The prescribed dose was 42.4 Gy, delivered in 16 fractions. No special breathing management was performed during simulation or treatment, but the patients were advised to maintain light normal breathing during irradiation. For CT-simulation and planning, patients were lying on a breast sloped board and a planning CT-scan was obtained with the patient in the treatment position, from the level of the mandible down to the diaphragm, with a 3 mm slice thickness. Room lasers and skin markers (setup tattoos) were used to ensure accurate and reproducible positioning. The breast was clinically marked with a wire prior to the CT-scan. For treatment, the patient setup was performed according to the skin-marks. Shifts in the anterior, lateral, and cranio-caudal (CC) directions were then applied according to the coordinates from the planning system. Anterior and lateral source-to-skin distance (SSD) measurements

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were taken and compared to the planned SSDs (with a one cm tolerance) as a secondary verification of isocenter position. Any discrepancy exceeding the one cm tolerance was investigated and corrected. After the initial laser setup, 2 orthogonal MV x-ray images were acquired, for 5 consecutive fractions; the x-ray images were taken randomly at any point in the breathing cycle. The displacement of the orthogonal MV x-ray images with respect to the orthogonal Digital Reconstructed Radiographs (DRR) was corrected after manual registration using bony landmarks (namely, the spine and chest wall) (**Figure 1**). The setup corrections included couch translations only; no couch rotations were used. The EPI of the medial tangential radiation fields were performed daily. The registration of the EPIs with respect to the corresponding DRRs was performed manually by a radiation oncologist (**Figure 2**). First, the EPIs were analyzed qualitatively by a radiologist. Then, displacements of the breast contour were recorded in both the antero-posterior (AP) and CC directions in the beam's eye view of the medial tangential fields (**Figure 2**). Also, shifts of the chest wall contour were recorded in the AP direction. All shifts were recorded by a radiation oncologist and cross-checked by a medical physicist. Next, the average setup error with standard deviation was calculated for each patient in both directions, for medial tangential fields. The setup errors were measured daily, using the electronic portal imaging system of the treatment machine (Beam View, Siemens Healthcare, Erlangen, Germany). One portal image of the medial tangential field was performed by the therapists during treatment delivery, so that no additional dose was given to the patient. To determine the setup variation, we generated the corresponding beam's-eye view (BEV) image from the planning system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA), showing the breast contour, the chest wall, the beam portal, and the planning isocenter. Each daily EPI was then overlaid and compared with the planning generated BEV image (**Figure 2**). Using this overlay, we determined the

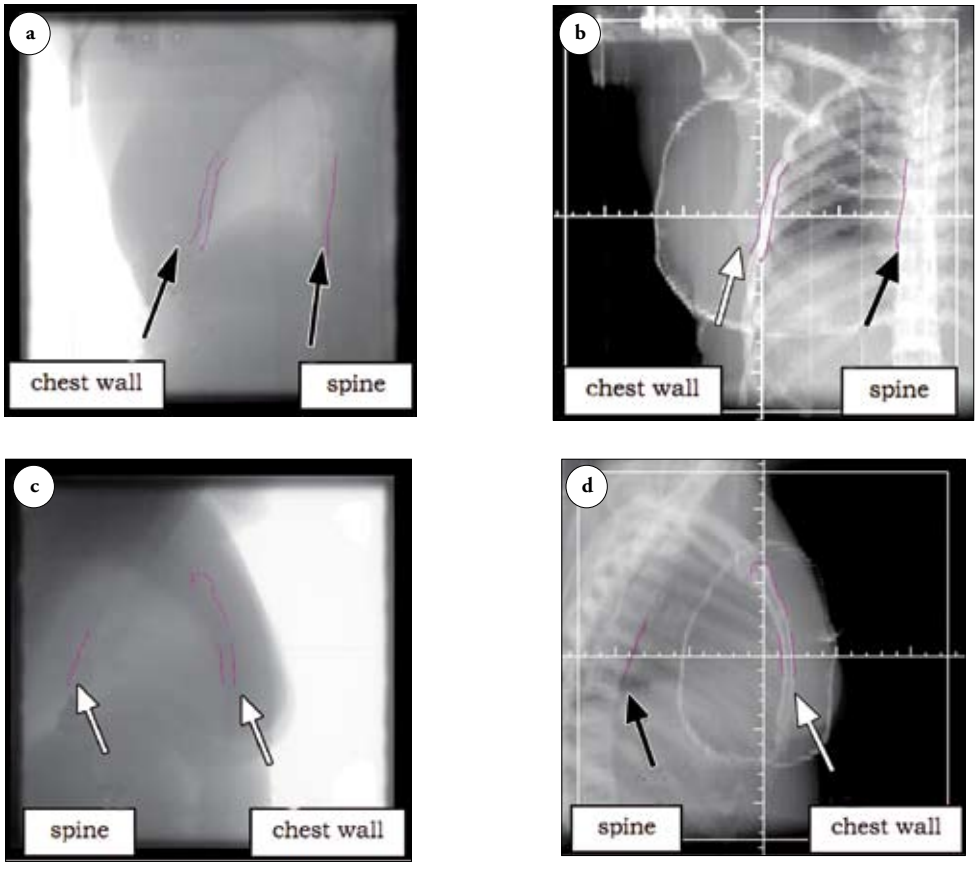

Figure 1 - Registration of the orthogonal megavoltage (MV) x-ray images with respect to the orthogonal digital reconstructed radiographs (DDR) using bony landmarks (the spine and chest wall) showing **a)** antero-posterior (AP) MV EPI, **b)** AP DRR, **c)** right lateral MV electronic portal images, and **d)** right lateral DRR.

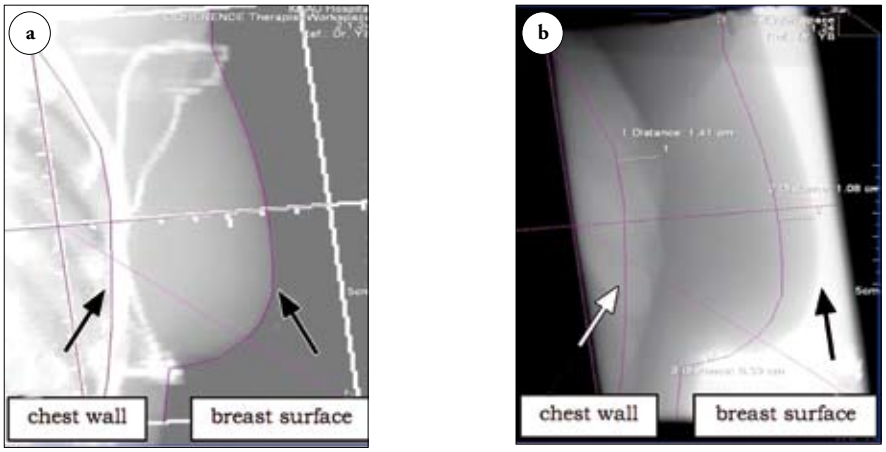

Figure 2 - Registration of electronic portal images (EPI) with respect to the digital reconstructed radiographs (DRR) showing **a)** planned treatment field DRR, and **b)** treatment field megavoltage EPI.

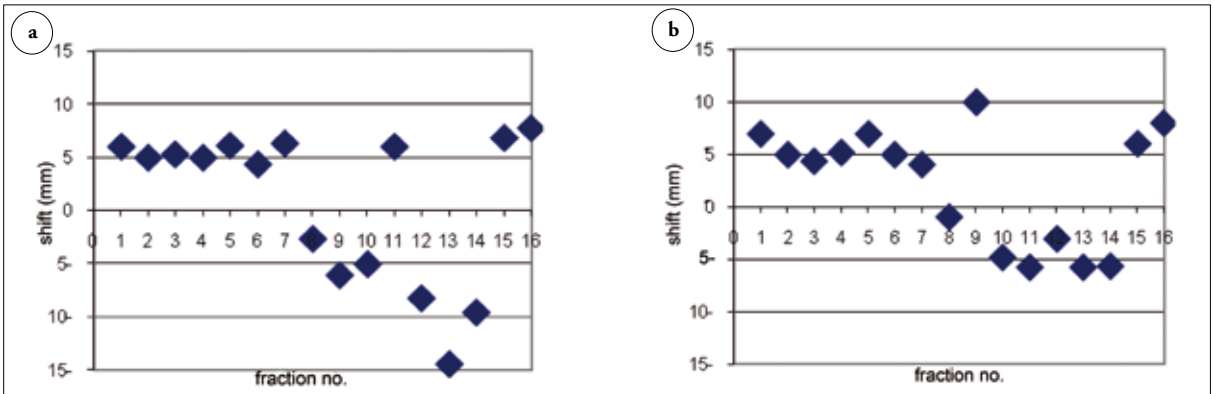

Figure 3 - Inter-fraction shift between the planned and treatment position of the breast surface showing **a)** antero-posterior shift, and **b)** cranio-caudal shift.

inter-fraction variations of the patient setup, for those fractions of the treatment when the patient setup was carried out on a skin marks basis, as well as for those fractions when the patient setup was carried out on an orthogonal EPIs basis.

To appraise the difference between the 2 studied treatment setups, the Wilcoxon pair test was applied. Data were considered statistically significant at $p<0.05$. The mean shifts and standard deviations (SDs) were calculated for each patient. The population systematic and random errors associated with the skin-mark setup, and with orthogonal EPI guidance were then calculated. The systematic error was calculated from the SD of all means, and the random error was calculated from the root mean square of all SDs. The calculation of these different parameters is summarized in **Appendix 1**.

We determined the CTV to PTV margins first by considering the margin recipe developed by van Herk et al,[18] that accounts for both systematic and random errors. This margin ensures that for 90% of the patients, 95% of the prescribed dose is delivered to the CTV and is calculated by: $2.5 \sum + 0.7 \sigma$ (Equation 1), where $\sum$ is the standard deviation of the distribution of the patient averages and accounts for the systematic errors in the setup, and σ is the average standard deviation of the day-to-day patient setup and accounts for random errors. Because in the case of SIB, the boost volume had already received background (whole breast) irradiation, the coefficient of 0.7 in front of σ is not applicable.[15,19] Considering a prescribed dose of 50 Gy to the whole breast and 10 Gy to the boost, and to ensure 95% of the total dose to the boost, only 70% of the boost dose needed to be delivered. Therefore, the coefficient in front of σ should be 0.3.[18,19] Thus, by assuming a 3D dose distribution, the margin recipe formula becomes: $2.5 \sum + 0.3 \sigma$ (Equation 2). Furthermore, because opposed tangential fields are used for the whole breast irradiation, the conformation will be perfect in 2D instead of 3D

Table 1 - Breast position variations (average values and standard deviations) for orthogonal electronic portal images (EPIs) and skin marks setup.

Setup	Breast shift (mm)			
	Anterior	Posterior	Cranial	Caudal
Orthogonal EPIs setup	4.6 ± 1.5 (max 12)	4.3 ± 3.7 (max 10.3)	4.5 ± 3.6 (max 8)	3.8 ± 3.5 (max 12)
Skin marks setup	6.1 ± 2.7 (max 12.5)	5.4 ± 2.7 (max 14.5)	5.8 ± 2.0 (max 10)	4.3 ± 2.5 (max 12.5)
P-value	0.009	0.008	0.004	0.020

and the coefficient 2.5 in front of ∑ becomes 2.15.[18,19] The systematic error ∑, random error σ, and margins for the breast PTV and boost PTV were calculated for the skin marks setup and bony anatomy setup.

Results. *Inter-fractional setup variations.* The shift between the planned and actual treatment of the breast surface was measured on each collected portal image in the AP and CC directions. A scatter plot of the daily measurements for one patient is shown in **Figure 3**, which illustrates several typical observations. First, the daily shift in both directions varies around approximately 10 mm, regardless of the duration of completed treatment. Second, it clearly shows that systematic shifts are present in both AP and CC directions, around which the daily setup errors are clustered. We have determined the inter-fraction variations due to patient translation and rotation, and breast motion/deformation, for those fractions of the treatment when the patient setup was carried out on an orthogonal EPIs basis, as well as for those fractions when the patient setup was carried out on a skin marks basis. We found that inter-fractional patient setup variations cannot be ignored, but can be significantly reduced if the orthogonal EPIs setup protocol is used ($p<0.05$). The results of the average shifts (as the mean of all means) and the related standard deviations, as well as the *p*-values, are shown in **Table 1**. Also, the shift between the planned and actual treatment of the chest wall was measured on each collected portal image in the AP direction and was used to evaluate inter-fraction changes in patient position throughout the treatment course. A scatter plot of the daily measurements of setup errors for one patient is shown in **Figure 4**.

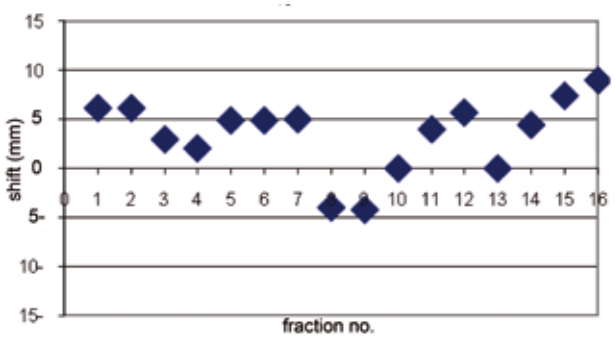

Figure 4 - Inter-fraction shift between the planned and treatment position of the chest wall.

Determination of margins for whole breast PTV and boost PTV. To calculate the necessary margins for whole breast PTV and boost PTV, inter-fractional errors are added up in quadrature. To estimate the required margins, the systematic and random errors for the 10 patients in AP and CC directions are considered and equations (1) and (2) are used. **Table 2** lists the systematic error ∑ random error σ, and margins obtained from our patient population, for the patient treatment setup carried out on an orthogonal EPIs basis, as well as for the setup carried out on a skin marks basis.

In the present study, the inter-observer variability in target delineation on CT-scans was not included in the margin recipe. However, this can be large,[18-20] and can have a significant impact on the systematic error ∑ and, consequently, in assessing correct margins.

Discussion. In the first part of this study, we determined the inter-fractional setup variation; the results show a clear systematic error in the patient setup with an average magnitude of 5.4 mm for a setup

Table 2 - Breast and boost setup uncertainties and required margins for orthogonal electronic portal images (EPIs) and skin marks setup.

Errors	Breast (mm)				Boost (mm)			
	Anterior	Posterior	Cranial	Caudal	Anterior	Posterior	Cranial	Caudal
Systematic setup error	4.6	4.3	4.5	3.8	4.6	4.3	4.5	3.8
Random setup error	2.3	1.2	3.4	1.3	2.3	1.2	3.4	1.3
Margins orthogonal EPIs setup	11.3	9.9	12.1	9.0	12.0	10.9	12.2	9.8
Systematic setup error	6.1	5.4	5.7	4.3	6.1	5.4	5.7	4.3
Random setup error	1.3	1.6	3.6	1.4	1.3	1.6	3.6	1.4
Margins skin marks setup	14.0	12.6	14.9	10.1	15.6	13.8	15.4	11.1

carried out on a skin marks basis, and an average of 4.3 mm for a setup carried out on an EPIs basis ($p<0.05$). The analysis of the systematic errors over the data of all patients included in this study shows that these errors are random, therefore not related to the setup itself. The determination of setup errors carried out in this study is based on the daily reproducibly of the patient contour, and therefore any distortions of the soft tissue may lead to a misestimating of setup error. In addition to the contour-based evaluation of the daily errors, we analyzed the position of the chest wall too. According to the variation of the chest wall position, it can be seen that there is a change that occurs with daily setup variation, resulting in changes in lung irradiated volumes.

As presented in the study method, the setup errors have not been measured 3-dimensionally. To have a 3D evaluation of the inter-fractional variations, we should have used an additional orthogonal EPI beam, which would have added radiation exposure to the lungs, and increased workload on the treatment machine. By deliberately using only treatment fields EPIs, we were unable to correct for setup errors in the direction of the beam axis. Although this is a limitation of our study, we consider that a setup error in beam axis direction only results in a different source skin distance, and the effect on the dose coverage is of minor importance.

Published studies have reported the use of various imaging modalities in order to assess the accuracy of patients setup for tangential breast radiotherapy.[14-16,21-25] This can be useful for measuring the amount of lung within the treatment field and for assessing coverage of the breast. Some of these studies have presented large random deviations of up to 2.3 cm,[21] therefore emphasizing the need for image-guidance in radiotherapy practice.

In the second part of this study, the margin formula of $2.5 \sum + 0.3 \sigma$ was used for the boost PTV.[18,19] However, the assumption that the boost region always receives background (whole breast) irradiation was made. Several different factors could also lead to different coefficient in front of the σ.[9,18,26] The most important include different irradiation schemes with different irradiation ratios between the boost and whole breast (namely, for APBI, $\sigma = 0.7$); a different penumbra width caused by various irradiation modalities (photons, electrons) and their energies; and an eccentrically located excision cavity (for example, close to the ribs or surface), compromising the assumption of an adequate background dose. Furthermore, if opposed fields are used, the conformation will be perfect in 2D instead of in 3D and the coefficient of 2.5 in front of $\sum$ would become 2.15.

Our values of $\sum$, σ, and margins are slightly higher than those presented in other published studies.[9,13,27,28] However, a detailed comparison is difficult, because different components of the geometric uncertainties were considered in the different studies. Also, different imaging modalities and technologies were employed in these studies. White et al[13] presented a Cone Beam CT (CBCT) based APBI setup correction using manual registration of the surface and chest wall, while Topolnjak et al[9] used an on-line CBCT-based SIB setup correction strategy. Furthermore, Weed et al,[27] as well as Kim et al[28] presented similar results using automatic detection of the clips implanted in the excision cavity. Having such a wide variety of approaches, it is difficult to correctly compare our values of setup variations against other published data. We consider that one of the factors directly affecting the value of patient setup variations in breast radiotherapy is the anthropomorphic characteristics of our female patients, such as large breast size, often pendulous. Another factor is the small number of patients data analyzed in this study, which might significantly alter the statistical results.

Due to the direct correlation between boost PTV margins and the systematic patient setup errors, it becomes obvious that there is a need to improve the accuracy of patient positioning, to decrease the CTV to PTV margins.[9,22-24] The use of a large margin will inevitably result in the irradiation of a large volume of normal tissue. Therefore, image-guided radiotherapy is essential to improve the accuracy of daily treatment setup. In particular, an imaging modality capable of identifying the lumpectomy cavity would be the ideal solution for SIB. Recent studies have shown that surgical clips placed in the cavity can serve as a good surrogate for the location and size of the cavity.[27]

The data presented illustrate the variation in the breast tangent treatment fields due to motion and setup error inherent in the delivery of a course of radiation therapy to the breast with tangent fields and slope breast board stabilization. Implementing Image Guided Radiation Therapy (IGRT) for SIB, as well as for any 3D-CRT technique, reduces the random and systematic setup error when compared with a skin-mark setup. This reduction will have consequential effects on the PTV margins. If correctly estimated and used in a margin recipe, these errors can be used to calculate the required PTV margins associated with each setup method.[13] To be conservative, a uniform margin of the boost PTV estimates for the setup using skin-marks can be calculated to be 15.6 mm isotropically, compared with 12.2 mm for the IGRT protocol. This indicates that a skin-mark setup, as described here, is sufficiently accurate for the safe delivery of SIB, provided that 15.6 mm PTV margins are maintained. It also suggests that PTV margins may be reduced if daily IGRT is performed.

An obvious limitation of this study is the small number of patient data included in analysis. We acknowledge that designing PTV margins based on the probability of correct target coverage, which is a statistical method, requires further investigations on a larger sample size, relevant for the size of patient population treated with SIB. Intra-fraction motion was not assessed by this study and this is another factor to be considered when designing appropriate PTV margins. Although this is another limitation of our study, since no assessment of respiratory motion has been performed, the setup errors reported include respiratory motion. However, a note of caution should be added: IGRT with radiographic modalities adds more radiation dose to the already high dose burden to the patient, in ways that are fundamentally different from the therapy itself. In a previous study we calculated the dose delivered to the patient by MV imaging modalities, for various sites.[29] We found that the maximum dose from orthogonal MV images of the mediastinum is approximately 10 ± 0.1 cGy/fraction and the dose to the lung approximately 7.9 ± 1.4 cGy/fraction. Considering the large field sizes used for imaging procedures (25 cm x 25 cm), the concern of a stochastic effect is raised, as well as the need for careful management of the IGRT procedures.

In conclusion, inter-fractional variations for whole breast irradiation have been studied based on EPIs for a selected group of patients. These variations were used to determine the CTV to PTV margin for SIB in breast irradiation. It was found that inter-fractional patient setup variations are significant, and contain both systematic, and random errors. These variations do not affect target coverage for whole breast irradiation, but they lead to a large CTV to PTV margin (for example, 15.6 mm) for SIB. The need for such a large margin indicates the importance of image guidance for SIB. The current study shows that there is significant day to day setup variation, and for high conformal 3D-CRT plans a daily positioning verification is necessary to ensure that the radiation dose is being correctly delivered to the PTV. Daily EPIs are a reliable correction strategy to keep the setup variations within acceptable tolerances.

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Appendix 1. Procedure used to calculate patient and population systematic and random deviations.

Upon treatment completion, patients' setup errors were analyzed by determining the systematic and random deviations. Systematic deviations are setup errors that occur throughout the course of treatment and which are mostly due to treatment preparation and treatment room inaccuracies (for example, laser misalignment, table shifts), while random deviations are day to day variations in patient setup (including internal organ motion). For an individual patient's setup errors, the mean m and standard deviations SD are generated (x_i: set-up error for fraction i and n: total number of fractions).

Patient j:

Systematic deviation: $$m = \frac{1}{n}\sum_{i=1}^{n} x_i$$

Random deviation: $$SD = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(xi - m)2}$$

For the whole population, M is the mean and Σ is the standard deviation of all patients' systematic setup errors (m_j: systematic deviation for patient j and N: total number of patients). The population's random deviation σ is obtained by calculating the root mean square of all patients' random deviations (SD_j: random deviation for patient j).

Population:

Systematic deviation: $$M = \frac{1}{N}\sum_{j=1}^{N} m_j \qquad \Sigma = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N}(mj - M)2}$$

Random deviation: $$\sigma = \sqrt{\frac{1}{N}\sum_{j=1}^{N}\left(SD_j\right)2}$$