



# Improving patient positioning and posture for breast cancer radiotherapy using DIBH and SGRT techniques by modifying fixation devices and tightening SGRT tolerances

Lauri Järvinen<sup>1,2</sup>, Marko Laaksomaa<sup>3</sup>, Mikko Björkqvist<sup>1,2</sup>, Jani Keyriläinen<sup>1,2,4</sup>

<sup>1</sup>Department of Medical Physics, Turku University Hospital and University of Turku, Turku, Finland

<sup>2</sup>Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland

<sup>3</sup>Department of Oncology, Tampere University Hospital, Tampere, Finland

<sup>4</sup>Department of Physics, Faculty of Science, University of Helsinki, Helsinki, Finland

## ABSTRACT

**Background:** Surface guided radiotherapy (SGRT) aids to place the patient in the correct position before radiotherapy. The aim of this retrospective observational study was to investigate how modifying patient fixation devices and tightening SGRT tolerances reduces residual errors and interfractional positioning variability in patients' position and posture for deep inspiration breath hold radiotherapy (RT) of breast cancer.

**Materials and methods:** The patient fixation devices were changed by introducing a 10° wedge-shaped foam cushion under the patients' back and rotating the previously used knee wedge to support the pelvic position more tightly. Additionally, the SGRT tolerance values were tightened from 8 or 12 mm to 5 mm. Patient Group A (n = 25) had had breast-conserving surgery and Group B (n = 25) mastectomy before RT. Residual errors of bony landmarks, breast outline and indicators of patient posture were retrospectively analyzed in a treatment planning system from 472 and 467 fractions before, and from 571 and 665 fractions after modifications for Groups A and B, respectively.

**Results:** Statistically significant improvements ( $p < 0.05$ ) in residual errors were found at the positions of the shoulder joint, T1 and T2 vertebrae (Group B), and the sternum (Groups A and B), as well as the rib cage (Group B) and the breast outline (Group A) in kV images. Systematic error for patient pitch decreased from 3.7 mm to 2.0 mm (Group A) and from 3.2 mm to 1.8 mm (Group B) ( $p < 0.05$ ).

**Conclusions:** The modifications improved patients' position and pitch.

**Keywords:** surface-guided radiotherapy; breast cancer; deep inspiration breath-hold; radiotherapy; image-guidance

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## Introduction

Radiotherapy (RT) is a common form of breast cancer treatment due to its reduction of recurrence after surgery of the tumour as well as lymph nodes containing metastases [1]. In the surgery, either

the breast tumour is removed with margins conserving the breast, or the entire breast is removed (mastectomy). In locoregional disease, in addition to the breast or chest wall, supraclavicular lymph node regions are also irradiated. In this case, positioning of the moving shoulder joint and thoracic

**Address for correspondence:** Lauri Järvinen, TYKS Turku University Hospital, Department of Medical Physics and Department of Radiation Oncology, P.O. Box 52 FIN-20521 Turku, Finland; e-mail: lauri.jarvinen@varha.fi

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spine must also be taken into account in the patient's positioning [2]. In left breast RT, the deep inspiration breath hold (DIBH) techniques increase the distance between the heart and the treatment regions [3], which is known to reduce the dose to the heart and thereby reduce the risk of cardiac disease caused by RT [4, 5].

In recent years, patient positioning with lasers and tattoo markings has been increasingly replaced by optical surface guidance [6] — surface guided radiotherapy (SGRT), where optical light reflected from the patient's body is used to form a 3D-image of the patient's skin. SGRT has been found to improve patient setup accuracy compared to lasers and tattoo marks for radiotherapy of breast cancer patients [7, 8]. One advantage of an SGRT-system is a free-breathing reference surface, acquired with an optical camera or computed tomography (CT) scanner, which aids in setting up the patient in the correct position. Moreover, monitoring the patient's position and posture by continuously updating real-time body contours, and guiding breath hold by tracking a virtual marker usually placed on the skin over the xiphoid process, are available. Utilizing retrospective analysis of patient motion provided by SGRT combined with anatomical imaging, site-specific treatment margins can be established [9]. The more the patient's position and posture are in line with the RT planning image, the less compromises are needed in orthogonal kV image-based matching during daily treatment, and the smaller setup margins for the clinical target volume are required [10]. With SGRT, it is known that the intrafractional patient setup accuracy is significantly better than the interfractional setup accuracy [11], which calls for a more repeatable patient setup procedure and daily image guidance. Furthermore, it has been shown in a multicenter study, that setup accuracy differs among clinics [12].

This retrospective observational study investigates the combined effect of modification of patient fixation devices, and tightening SGRT tolerances to reduce interfractional positioning variability and residual errors of anatomic bony landmarks for two groups of patients i.e., DIBH RT after breast-conserving surgery and mastectomy. All changes in patient fixation devices and SGRT tolerances stemmed from reported practical clinical experience [12], and in order to improve radiotherapy

treatment of the patients, they were implemented simultaneously. The authors are not aware of a similar study. Residual errors and variation in patient postures after daily image guidance were analyzed both before and after the changes.

## Materials and methods

### Patient selection

No ethical approval was required for this retrospective study, which included 25 post-breast-conserving surgery (Group A) and 25 post-mastectomy (Group B) patients who received RT to the breast or chest wall area with nodal involvement using DIBH in 2019. After the modification of patient fixation devices and SGRT tolerances in 2020, there were 20 patients in each group including a total of 472 and 467 analyzed fractions after setup changes for Groups A and B, while 571 and 665 fractions were analyzed using the initial setup and tolerances for Groups A and B, respectively.

### Planning CT

All patients were imaged using a Toshiba Aquilion LB (Canon Corp., Tokyo, Japan) CT scanner with 2-mm slice thickness. Successful breath holding in a 3 mm vertical gating window and a reproducible expiratory baseline were prerequisites for DIBH treatment. The Sentinel™ (C-RAD AB, Uppsala, Sweden) SGRT-system [13] was used to set a virtual primary gating point over the xiphoid process. Patients were coached through wireless Bluetooth goggles (C-RAD AB, Uppsala, Sweden), illustrating the vertical movement of the primary gating point. Free-breathing positioning reference surfaces were acquired using Sentinel™ camera. No tattoo marks were used.

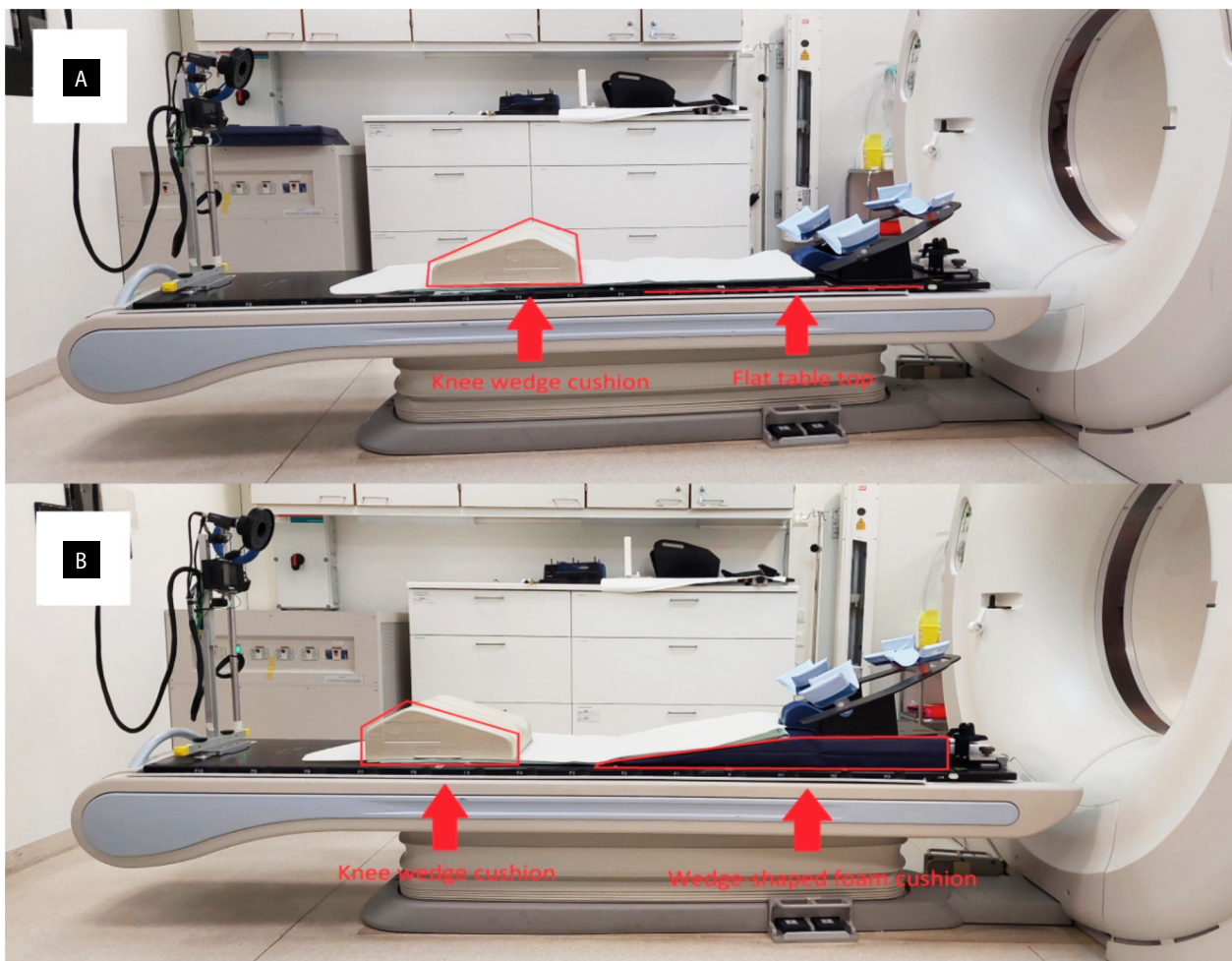
### Modification of patient fixation devices and optical surface guidance tolerances

Initial patient positioning equipment consisted of a Civco (Civco Medical Solutions, Coralville, IA) breast board attached to the couch with a bar and an unattached Civco knee wedge cushion under the knees to support pelvic position. In addition, the patients held onto a grip ring to facilitate the position of the arms above the head. The change consisted of introducing a wedge-shaped foam cushion WingSTEP MCT Wedge with 10° wedge (Innovative Technologie Völp GmbH, Innsbruck,

Austria) and turning the knee wedge around to support the pelvic position more tightly, preventing patients from sliding down the wedge-shaped cushion. The changes in the patient fixation equipment were identical in both the CT and RT rooms. The initial (a) and modified (b) fixation devices are shown in Figure 1. In the treatment rooms, a Catalyst HD version 5.3.4 (C-RAD AB, Uppsala, Sweden) SGRT-system [14] was used to monitor the patient's position, immobilisation and DIBH level during RT. The tolerance of the Catalyst surface in patient positioning was reduced to 5 mm in both Groups A and B, as this has been reported in the literature [15, 16]. Before reduction, the tolerance was either 12 mm (for the first 9 patients) or 8 mm (for the next 16 patients) in Group A. In Group B, initial tolerances were 12 mm (for the first 17 patients) or 8 mm (for the next 8 patients).

### Treatment workflow

The initial position of the couch in the first treatment fraction was set according to the plan isocenter for vertical and lateral directions, and to 120 cm for the longitudinal direction. The rest of the patient positioning was carried out using the free-breathing reference surface captured by the Sentinel™ camera from a volume of interest including the thorax region, chin and proximal parts of the arms. When all three patient rotations were positioned accurately within two degrees according to the Catalyst system, the radiation therapists performed automatic couch shifts and manual patient positioning according to the Catalyst's instructions. Expiratory baseline was recorded during free-breathing using the Catalyst. In addition, a new treatment reference surface for the current fraction and orthogonal kV images



**Figure 1.** Initial (A) and modified (B) fixation devices of breast cancer patients on the computed tomography couch. A Civco breast board and knee wedge cushion can be seen on the couch

was acquired with the patient's breath-hold level (BHL) inside the 3 mm gating window.

Online matching of orthogonal kV images was primarily based on the positions of the sternum and chest wall, while the humeral head and vertebrae were also taken into account after locating the primary landmarks. The treatment reference surface was updated after matching, if the couch position was shifted. During the first treatment session, the couch position was permanently saved to be used as initial position for latter fractions. Four to five tangential kV images in total were taken to confirm the correct position of the rib cage and breast outline primarily during the first week of treatment. The imaging parameters of the templates used varied between 80–120 kV and 2.0–6.4 mAs depending on the thickness of the patient in the X-ray path. The setup tolerances used were 5, 7 and 10 mm for BHL, bony structures and breast outline, respectively. Patients were treated on Varian TrueBeam linear accelerators (Varian Medical Systems Inc., Palo Alto, CA).

### Residual positioning errors

The isocenter residual errors were retrospectively read from the couch shift values of the online match. Residual positioning errors of the individual landmarks (as defined by Laaksomaa et al. [17]) after daily orthogonal kV-imaging based matching were retrospectively obtained in the Offline review workspace of Eclipse Treatment Planning System (TPS). The acquired kV-images were manually moved from the treatment position to exactly match the anatomical landmark in the digitally reconstructed radiograph image, and the given shift was read. The tangential kV images were used to evaluate residual rib cage and breast outline errors, the latter of which was evaluated only for patient Group A with RT after breast-conserving surgery. The systematic error for a group of patients is an indication of the spread of individual mean errors around the overall population mean. It is calculated as the standard deviation of the distribution of the mean errors for each individual patients, i.e. individual systematic errors. The random error for a group of patients is defined as the mean of all the individual random errors, i.e. interfractional daily setup errors for individual patients.

The differences between two anatomical landmarks describing the change in patient posture

were calculated simply by subtracting the residual error of the latter landmark from the residual error of the former one. The landmark differences describing the patient's posture were T8–10 vertebrae and sternum, T1 and T8–10 vertebrae, and T1 vertebra and shoulder joint. Vertical and longitudinal differences between the T8–10 vertebrae and sternum indicate the degree of lung filling, or BHL, and pitch, respectively, while the differences between the T1 and T8–10 in all directions indicate the straightness of the thoracic spine. The repeatability of the arm posture is obtained from the difference between the T1 vertebra and shoulder joint.

### Limitations

In this study, the patients in both groups A and B were divided into initial and modified subgroups based solely on the time of their treatment. Even though the design of the study was not randomized, a comparison between the subgroup after intervention and the control group was carried out. There is also a potential unconscious bias in favor of the modified subgroup during offline matching due to a single, although experienced, observer.

### Statistical analysis

Statistical analysis was used to evaluate the significance of the difference between the residual positioning errors with the two different patient fixation methods, including the change in SGRT surface tolerance from 8–12 mm to 5 mm. The F-test was used to test the systematic residual errors of the two groups of patients (test for equality of variances) [18], and the T-test was used to test the random residual errors (test for equality of means) [19]. A p-value of less than 0.05 was considered statistically significant.

## Results

### Comparison of residual error in isocenter and bony landmarks

Table 1 depicts the statistically significant residual errors in isocenter position before orthogonal kV imaging and in bony landmarks after orthogonal kV imaging in Group A. The full table is given as a supplementary material. Statistically significant improvements in systematic residual errors after imaging-based matching include sternum placement in the antero-posterior (AP) direction

**Table 1.** Comparison of patient position in breast cancer patients with axillary lymph node inclusion after breast-conserving surgery (Group A) as systematic and random residual errors ( $\Sigma \pm \sigma$ ) in mm after orthogonal kV imaging before (2019) and after (2020) setup changes. Only statistically significant differences are shown

	2019			2020		
	AP	CC	LR	AP	CC	LR
Sternum	1.6 ± 1.6			0.8 <sup>a</sup> ± 1.4		
Rib cage/sternum average		1.7 ± 1.6			1.5 ± 1.9 <sup>b</sup>	
	CC		AP/LR	CC		AP/LR
Breast outline tangential		2.1 ± 1.7			1.1 <sup>a</sup> ± 1.7	

AP — anterior-posterior; CC — cranio-caudal; LR — left-right; <sup>a</sup>Significant difference (F-test;  $p < 0.05$ ) in the systematic residual error between 2019 and 2020; <sup>b</sup>Significant difference (t-test;  $p < 0.05$ ) in the random residual error between 2019 and 2020

**Table 2.** Comparison of patient position in breast cancer patients with axillary lymph node inclusion after mastectomy (Group B) as systematic and random residual errors ( $\Sigma \pm \sigma$ ) in mm after orthogonal kV imaging before (2019) and after (2020) setup changes. Only statistically significant differences are shown

	2019			2020		
	AP	CC	LR	AP	CC	LR
T1 and T2 vertebrae	2.0 ± 2.1	1.9 ± 1.8	1.2 ± 1.7	1.2 <sup>a</sup> ± 1.7 <sup>b</sup>	0.7 <sup>a</sup> ± 1.3 <sup>b</sup>	0.7 <sup>a</sup> ± 1.4 <sup>b</sup>
Sternum	1.3 ± 1.7			1.0 ± 1.2 <sup>b</sup>		
Shoulder joint			2.4 ± 2.0			1.2 <sup>a</sup> ± 1.7
	CC		AP/LR	CC		AP/LR
Rib cage tangential		1.1 ± 1.0	1.7 ± 1.1		0.7 <sup>a</sup> ± 0.9	1.0 <sup>a</sup> ± 1.2

AP — anterior-posterior; CC — cranio-caudal; LR — left-right; <sup>a</sup>Significant difference (F-test;  $p < 0.05$ ) in the systematic residual error between 2019 and 2020; <sup>b</sup>Significant difference (t-test;  $p < 0.05$ ) in the random residual error between 2019 and 2020

and tangential breast outline in the cranio-caudal (CC) direction. However, the random residual error of the average position of the rib cage and sternum in the CC direction increased with a single statistically significant difference in patient positioning after setup changes. No statistically significant changes in isocenter residual errors, i.e. couch shifts after orthogonal kV imaging based matching were observed.

Table 2 shows the statistically significant residual errors in the position of the isocenter before orthogonal kV imaging and bony landmarks afterwards in mastectomy patients (Group B). The full table is given as a supplementary material. Compared to the data of the patient Group A shown in Table 1, more residual errors decreased statistically significantly within Group B, especially at the T1 and the T2 vertebrae, for which every systematic and random residual error decreased. Other statistically significant improvements were the systematic residual error changes in the left-right (LR) direction in the shoulder joint, in the AP/LR direction in the tangential rib cage, and in the CC direction in the tangential rib cage. The random residual

error of the sternum decreased in the AP direction. Again, there were no significant changes in the isocenter residual errors.

### Comparison of patient posture and tolerance exceedings' percentages

Table 3 presents the statistically significant residual errors of the patient's posture by comparing two anatomical landmarks, which allows the evaluation of DIBH-induced rotations and changes in patient's posture. The full table is given as a supplementary material. The residual errors of the latter landmark are subtracted from the errors of the former landmark. The difference in the AP direction between T8–10 vertebrae and sternum represents the filling level of the lungs (i.e. BHL) [20], while T1–T8–10 represents the straightness of the spine or rotations of the patient. Finally, T1 — shoulder joint describes how well the arm and shoulder stay in place. Statistically significant improvements occurred mainly in systematic errors in the CC direction. In both patient groups, the systematic error in T8–10 — sternum (CC) decreased in 2020. In Group B, the random rotation error was smaller in

**Table 3.** Comparison of patient posture as a difference between two anatomical landmarks in breast cancer patients with axillary lymph node inclusion after breast conserving-surgery (Group A) and mastectomy (Group B) as systematic and random residual errors ( $\Sigma \pm \sigma$ ) in mm after orthogonal kV imaging before (2019) and after (2020) setup changes. Only statistically significant differences are shown

	2019			2020		
	AP	CC	LR	AP	CC	LR
<b>Group A</b>						
T8–10 — sternum		3.7 ± 2.5			2.0 <sup>a</sup> ± 2.2	
T1 — shoulder joint			1.9 ± 1.8			2.6 <sup>a</sup> ± 1.9
<b>Group B</b>						
T8–10 — sternum		3.2 ± 2.5			1.8 <sup>a</sup> ± 2.2	
T1–T8–10		0.8 ± 1.1	1.2 ± 2.0		0.5 <sup>a</sup> ± 0.9	1.0 ± 1.6 <sup>b</sup>
T1 — shoulder joint		4.2 ± 3.1			2.4 <sup>a</sup> ± 2.3 <sup>b</sup>	

AP — anterior-posterior; CC — crano-caudal; LR — left-right; <sup>a</sup>Significant difference (F-test;  $p < 0.05$ ) in the systematic residual error between 2019 and 2020; <sup>b</sup>Significant difference (t-test;  $p < 0.05$ ) in the random residual error between 2019 and 2020

the latest data for T1–T8–10. In addition, Group B showed improvements in shoulder position in the CC direction for both systematic and random errors.

Table 4 shows percentages of anatomical landmarks exceeding the tolerance of 4 mm (3 mm for T8–10 — sternum). Instead of a tolerance of 7 mm that is used in our clinic as a tolerance value for offsets of anatomical landmarks, the stricter 4 mm tolerance was chosen to demonstrate landmark positioning changes to a higher degree of accuracy. The direction in which the fewest couch shifts out of tolerance were seen was the LR direction. Out of tolerance shifts decreased in both groups at the sternum and shoulder joint and at the T1 and T2 vertebrae in Group B. In less than 1% of all the treated fractions, the rib cage exceeded the 4 mm tolerance in the LR direction. The setup changes clearly reduced the number of fractions exceeding the T8–10 — sternum tolerance in the CC direction (pitch), but not in the AP direction (BHL).

## Discussion

Surface imaging provides guidance for correcting the patient’s posture [9]. On the other hand, the addition of SGRT for initial patient positioning did not reduce the set-up errors in the study of Peninkhof et al. [21], which is why the fixation devices and SGRT margins need to be taken into account for improved patient positioning. Kapanen et al. [22] managed to reduce systematic residual errors maximally by 49.8 % after several changes in patient setup process for RT of head and neck cancer

patients. The implemented changes of this study to the patient fixation devices and SGRT tolerances of DIBH SGRT for a limited number of breast cancer patients seem to have improved the positions of several bony landmarks and posture indicators shown in Tables 1–3, especially after mastectomy. Even though our results cannot be generalized to every DIBH treatment of breast cancer due to relatively small sizes of the study groups, they are consistent with the results of Gnerucci et al. [23], who discovered that it is possible to reduce the occurrence of higher SGRT shifts by selecting a lower threshold value for surface tolerance. We did not find any improvements for the accuracy of the isocenter. However, this is less of a concern in daily image-guided RT.

In this study, a free-breathing reference surface captured by Sentinel™ camera was used for daily positioning. For the isocenter, a new free-breathing surface for patient positioning, which is taken after couch shifts based on orthogonal kV imaging, could improve the accuracy of the treatment isocenter position. Laaksomaa et al. [24] used the first three fractions to find the optimal SGRT surface. The reference surface acquired with a single Sentinel™ camera contains holes due to limited field of view and CT gantry blocking some parts of the body, while the three Catalyst cameras in the treatment room can record a more uniform surface. The random residual errors for the isocenter are the smallest in the LR direction, which is the most accurate part of surface guidance in patient positioning. Respiratory movements do not interfere with this orientation, and the position of

the cameras on the ceiling above the patients allows the cameras to see the lateral ends of the body contours more clearly than the anterior or CC surfaces perpendicular to the cameras. Reducing the surface tolerance from 8 or 12 mm to 5 mm did not reduce the isocenter residual error in the AP direction.

The residual errors shown in Table 1 for patients after breast-conserving surgery (Group A) decreased statistically significantly for the systematic errors of the sternum in the AP direction and the breast outline in the CC direction. It has been reported, that a stable breath hold-level alone does not guarantee the correct position of the breast [25]. Our findings indicate that the outline of the entire breast is reproduced better if the patients are in a more upright position, where the gravity pulls the breast downwards, thus decreasing the uncertainty of the patient position and posture in the target region. Moreover, a tilted breast-board [15] and low couch positions [7] are beneficial for the SGRT cameras due to better visibility. A more precise placement of the sternum in orthogonal kV image matching may be due to the prioritization of the sternum when matching in the AP direction. This interpretation is supported by the increasing systematic residual error in BHL (the AP direction of T8–10 — sternum) for Group A, as shown in Table 3.

For T1 and T2 vertebrae, sternum, shoulder joint, and rib cage, there were several improvements for systematic and random residual errors in the orthogonal images of Group B after setup changes, as shown in Table 2. Many of the improvements are interrelated and indicate a more reproducible patient posture. For example, the random residual error of the sternum in the AP direction and the systematic residual errors of the rib cage in the CC direction and the AP/LR directions combined in the tangential images indicate that the chest is positioned more accurately with tighter Catalyst tolerances and new fixation setup. This makes the delivered lung dose closer to the dose volume histogram values provided by the TPS. A more accurate positioning of the shoulder and the T1 and T2 vertebrae improves the dose coverage of the locoregional lymph nodes. Also, it has been reported that surface-guided correction of the arm posture improves the breast position [15, 26].

As shown in Table 3, most of the significant improvements in patient posture occurred in Group B

patients. According to the results, arm posture (indicated by T1 — shoulder joint) and spine straightness (indicated by T1–T8–10) have improved in Group B, which indicates improved coverage for lymph node regions. T8–10 — sternum indicating BHL in the AP direction and pitch in the CC direction shows that pitch is systematically improved in both groups A and B, which is known to spare the heart [27]. We suggest that a wedge-shaped foam cushion under patients systematically improves the reproducibility of patient pitch compared to a flat supine position. Because the BHL in the lateral kV image has a tolerance of 5 mm in our clinic, these residual errors have not resulted in further guidance for the patient to breathe. BHL can be improved by adjusting the distance between baseline and gating window to obtain an optimal adjustment of the correct distance between the thoracic vertebrae and sternum with the lateral kV image [28].

As can be seen from Tables 1–3, more improvements in systematic and random residual errors were observed for Group B than for Group A. It appears that more deformable soft tissue within the volume of interest reduces the accuracy of the Catalyst to guide patient positioning [16]. One source of error could be the skin coverage of the Sentinel™ camera, if breast tissue blocks the view of the clavicle and shoulder area.

The data in Table 4 on the 4 mm (3 mm for T8–10 — sternum) exceedances for many of the anatomic landmarks and patient posture indicators presented earlier in this study shed light on the utility of optical surface guidance. A clinical tolerance of 7 mm for bony structures has rarely been exceeded, which is why a stricter tolerance was chosen. The table shows that the residual errors for most of the treated fractions remain below 4 mm indicating high level of positioning repeatability in general.

Later, our workflow has been improved by acquiring new positioning reference surfaces during the first treatment fraction after position and posture have been accepted by online matching based on orthogonal kV imaging. Moreover, in addition to the rotations and translations suggested by Catalyst, the lights projected on patient's surface, which indicate that body parts are too high or low, are more systematically utilized. The next step could be more systematically monitoring that the baselines of each patients' breathing curves match with

**Table 4.** Percentages of anatomical landmarks exceeding the tolerance of 4 mm (3 mm for T8 — sternum) in breast cancer patients with axillary lymph node inclusion after breast conserving surgery (Group A) and mastectomy (Group B) after orthogonal kV imaging before (2019) and after (2020) setup changes. Isocenter refers to the couch shift that radiation therapists (RTTs) perform based on orthogonal kV imaging after positioning the patient using Catalyst

Group A	2019			2020		
	AP	CC	LR	AP	CC	LR
Isocenter	34	37	18	35	39	23
T1 and T2 vertebrae	24	9	3	17	9	5
Sternum	10	28		2	18	
Shoulder joint		26	13		18	13
Rib cage orthogonal		8	0.2		11	1
Rib cage/sternum average		8			10	
T8 — sternum	16	44		26	23	
		CC	AP/LR		CC	AP/LR
Rib cage tangential		4	4		7	5
Group B	AP	CC	LR	AP	CC	LR
Isocenter	31	40	20	42	34	22
T1 and T2 vertebrae	17	13	5	6	1	3
Sternum	12	26		3	15	
Shoulder joint		29	23		16	7
Rib cage orthogonal		8	0.6		6	0
Rib cage/sternum average		11			9	
Rib cage tangential	5	3		4	1	
T8 — sternum	19	42		19	25	
		CC	AP/LR		CC	AP/LR
Rib cage tangential		0/3	0/5			

AP — anterior-posterior; CC — cranio-caudal; LR — left-right

the actual curves to reduce patient tension and erroneous positions. Even though the residual errors have been decreased, daily image guidance is still needed because the patient setup errors differ substantially between treatment fractions.

## Conclusion

Modifications of patient fixation devices and optical surface guidance tolerances have mostly improved patients' positions and postures for this observational study. In Group B, statistically significant improvements were observed in residual errors at T1 and T2 vertebrae, sternum and shoulder joint positions on orthogonal kV images and at rib cage on tangential kV images. In Group A, the residual errors decreased for sternum and breast outline. For posture, pitch was improved for both groups, which is important in heart sparing. More reproducible patient position and posture can lead

to healthy tissue sparing by enabling smaller clinical target volume (CTV)–planning target volume (PTV) margins.

## Ethical approval

Ethical approval was not necessary for the preparation of this article.

## Conflict of interest

Authors declare no conflict of interests.

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## Author contributions

L.J.: main responsibility for writing the manuscript and reviewing the literature. Collection and interpretation data; M.L.: main responsibility for analyzing the data. Writing the manuscript, literature

review, data interpretation and study planning; M.B.: study planning, data collecting, writing the manuscript; J.K.: study planning, writing the manuscript.

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