A Simple and Cost-effective Technique for Deep Inspiration Breath-hold Radiotherapy in Left-sided Breast Cancer Patients: A Retrospective Study

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Research

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Abstract

Background: Deep inspiration breath-hold (DIBH) radiotherapy is effective but requires specific devices for tracking the respiratory cycle or surface motion. There are some reports of DIBH without such devices. However, to the best of our knowledge, no study has evaluated all three components which are: setup accuracy, dose assessment, and treatment time. We evaluated the accuracy, effect of dose reduction on organs at risk (OARs), and the treatment time of our DIBH technique, which avoids the use of such devices.

Methods: We analyzed 64 left-sided early breast cancer patients. Three-dimensional conformal radiotherapy treatment plans of 42.56 Gy in 16 fractions were created in free-breathing (FB) and DIBH settings. Thirty patients were evaluated for inter- and intra-fractional displacement. The treatment room entry-to-exit times were measured and retrospectively compared with those of 44 right breast cancer patients who received FB radiotherapy (Right-FB) in the same period. The volumes and dose metrics of the clinical target volume (CTV) and contoured OARs (HEART, left anterior descending artery [LAD], and LUNG) were compared between FB and DIBH.

Results: The average inter-fractional, intra-fractional, and overall setup displacement were 2.32 ± 1.30, 0.55 ± 0.43, and 2.46 ± 1.24 mm, respectively. Compared to Right-FB, the medians of entry-to-exit times slightly increased in DIBH (9 vs 7 minutes, $P = 3.95e^{-23}$). The LUNG volume in DIBH was 1.58 times larger than that in FB, but other volumes were not statistically different. Compared to FB, the median HEART, LAD, and mean LUNG doses decreased significantly in DIBH: 1.67 vs 0.71 ($P = 9.72e^{-15}$), 13.0 vs 2.3 ($P = 6.65e^{-15}$), and 2.42 vs 2.03 ($P = 6.80e^{-8}$) Gy, respectively. CTV doses were not statistically different.

Conclusions: With only minor setup errors, this simple and cost-effective DIBH technique is a feasible method. It can be easily tested for new facilities and is expected to accelerate the further clinical implementation.

Trial registration:

Background

Breast cancer is the most diagnosed malignancy in women. The current estimated worldwide incidence of breast cancer is 2.09 million, with 627,000 deaths approximately [1]. With the increasing prevalence of breast cancer and the long-term survival of patients due to advances in treatment methods, measures against late adverse events have become increasingly important. Whole breast radiotherapy following breast conservation therapy reduces locoregional recurrence and deaths from breast cancer [2]. Some studies have shown that left-sided breast cancer patients suffer from late cardiac toxicities after radiation therapy [3–6]. Further, there are reports about the relationship between heart dose and severe cardiac toxicities [7–10]. However, modern breast cancer radiotherapy has substantially decreased cardiac mortality [11, 12].

Deep inspiration breath-hold (DIBH) is an effective and widely used method for reducing heart dose irradiation [13–17]. DIBH radiotherapy (DIBH-RT) is generally performed with specific devices for monitoring the respiratory cycle or for surface tracking, such as real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA), Catalyst™ (C-Rad, Uppsala, Sweden), and AlignRT® (VisionRT, London, Great Britain). Although these devices are reliable, accurate, and can use respiratory-gated radiotherapy, some of them are expensive and complicated to operate. The device needs to trace the chest excursion in the respiratory cycle with deep inspiration, note the maximum and minimum coordinates of the wave-form, and need to make the upper and lower thresholds to shut-off the treatment beam automatically [18, 19]. Medical staff need to coach patients on how to breathe deeply and hold their breath, which is estimated to require an additional 30–60 minutes [20, 21]. To reduce complexity, a simple DIBH method was proposed by Bartlett et al. [22]. We have modified the existing DIBH technique with reference to previous reports [22, 23, 29]. There are some reports about DIBH breast radiotherapy [13-23, 29]. Some reports focused on setup accuracy, while some focused on the effect of the dose reduction on the heart. However, to the best of our knowledge, no study has evaluated all three components which include: setup accuracy, dose assessment, and treatment time. The purpose of this study was to assess the accuracy and reproducibility of our DIBH technique, to evaluate its effect on dose reduction to organs at risk (OARs), and to compare the treatment time with the free-breathing (FB) treatment in patients with left-sided early breast cancer.

Methods

Patient selection

This study was approved by our institutional review board. All the patients obtained written informed consent. Patients with histologically confirmed invasive ductal carcinoma or carcinoma in situ in the left breast who underwent breast-conserving surgery and DIBH-RT at our institution from June 2018 to March 2020 were included. Patients who underwent post-mastectomy radiotherapy or regional lymph node irradiation were excluded.

Treatment planning

The patients were placed in the supine position on a wing board, with both arms overhead. They were instructed to inhale, then exhale, then take another deep breath and hold it in for approximately 15 seconds. We marked the midline of their chest with ink and measured how far they were moving from the free breath position; this information was recorded. Simultaneously, we checked the reproducibility of the deep inspiration position, the duration that the patients could hold their breath, and whether they were bending or twisting the torso during deep inspiration. Planning kilovoltage computed tomography (CT) scans were performed for DIBH techniques (CT1). The CT slice thickness was 3 mm. We obtained 3 additional CT scans (CT2, CT3, and CT4) consecutively. CT2 and CT3 were taken to evaluate the internal margin of the DIBH positions. The milliampere-seconds of CT2 and CT3 were at 1/3 of CT1, and the treatment plan was performed at CT1. CT4 was taken with the patient free-breathing to compare between

the FB plan and the DIBH plan. Laser-guided reference marks were drawn on the patient's chest. The reference marks were composed of 2 horizontal lines (an FB line and a DIBH line) and an anterior midline mark. When prepping the patient, the laser was first aligned with the FB line. The patient was then instructed to take a deep breath-hold so that the laser was aligned with the DIBH line and the light field did not exceed the anterior midline (Fig. 1).

Contouring and dose planning were carried out with RayStation ver6 (RaySearch Laboratories AB, Stockholm, Sweden) for FB and DIBH-CT. Clinical target volume (CTV) for the left breast was defined according to the consensus guidelines [24]. In DIBH, CTV was created from each of the three DIBH CTs, and the overlapping target volume was defined as the internal target volume (ITV). Planning target volume (PTV) included CTV or ITV with a 5-mm margin in all directions. The prescription dose for PTV was 42.56 Gy in 16 fractions using the Varian TrueBeam system (Varian Medical Systems, Palo Alto, USA). The delineated OARs included the lungs (LUNG), heart (HEART), and left anterior descending artery (LAD), which were contoured according to the heart atlas validation study with the same CT window level and width in all CT scans [25]. Both FB and DIBH treatment plans were created at the same time before the start of the treatment for consistency of plans. Treatment planning of FB-CT and DIBH-CT was 3-dimensional conformal radiation therapy (3D-CRT). All plans consisted of 2 opposing tangential beams and 2 additional beams using the field-in-field technique. This was not only to improve the target dose coverage and homogeneity, but also to reduce the patient's breath-holding time during each beam. To minimize measurement bias, the two treatment plans were created so that their contours were always contrasted, and their volumes were almost the same. Further, the two plans were restricted to have almost the same beam angle connecting from the midline of the patient's chest to the mid-axillary line, and the multileaf collimator (MLC) margin was also unified.

The dose metrics of CTV, HEART, LAD, and LUNG contours were compared between the DIBH and FB plans. All contouring and treatment plans were reviewed by 2 senior radiation oncologists and 1 medical physicist. Dose-volume histograms were calculated using MIM Maestro (MIM Software, Inc., Cleveland OH, USA). The mean doses of all contours, doses of 50% and 95% CTVs (D50, D95), and volumes of LUNG receiving 20 Gy (V20) were calculated.

Treatment

Treatment was begun after setting up the alignment mark at the time of irradiation, instructing on deep inspiration breath-hold, and confirming that the laser and DIBH lines matched. The patient's thoracic motion was monitored with a treatment room camera. Each patient was confirmed initial alignment with MV portal imaging on the first irradiation. If the setup reproductivity seemed poor, we checked in some fractions. During each irradiation, we also compared cine images on an electronic portal imaging device (EPID) with digitally reconstructed radiography (DRR) images to minimize the isocenter positioning errors (Fig. 2). If the radiologist in charge of irradiation felt that the laser and the chest surface mark were off by 3 mm or more, the irradiation was terminated.

To evaluate the total time required for treatment, the time to enter and exit the treatment room (entry-to-exit time) were recorded. We also recorded the beam-on time which was determined by the ratio of the total monitor units (MU) to the dose rate of 600 MU/minutes. We also retrospectively compared the entry-to-exit time of DIBH-RT with that of right breast cancer patients treated with the same treatment device in FB (Right-FB) from 2018 to 2020. Data were expressed as medians and interquartile ranges (IQRs).

Post-irradiation setup assessment

A total of 30 patients initially treated in this study were selected to measure the actual inter-fractional and intra-fractional displacement to evaluate the accuracy and reproducibility of our DIBH technique. The inter-fractional displacement was measured by comparing the EPID image obtained at the beginning of each irradiation with the DRR reference image. The intra-fractional displacement was measured by comparing the cine-EPID images from the first frame with the last frame at each irradiation. The motion range in the anterior–posterior direction (D_X) and cranio–caudal direction (D_Y), as well as the 2-dimensional (2D) displacement (D_{2D}), were calculated for all contours (CTV, HEART, LAD, and LUNG) as follows:

$D_{X\_inter} = X_{EPID\_initial} - X_{DRR}$; $D_{Y\_inter} = Y_{EPID\_initial} - Y_{DRR}$; $D_{X\_intra} = X_{EPID\_end} - X_{EPID\_initial}$; $D_{Y\_intra} = Y_{EPID\_end} - Y_{EPID\_initial}$; $D_{2D\_inter} = \sqrt{(D_{X\_inter}^2 + D_{Y\_inter}^2)}$; $D_{2D\_intra} = \sqrt{(D_{X\_intra}^2 + D_{Y\_intra}^2)}$; $D_{2D\_ALL} = \sqrt{(D_{2D\_inter}^2 + D_{2D\_intra}^2)}$. Data were expressed as the mean value ± standard deviation (SD). We defined D_{2D_ALL} + 2SD as the required setup margin. All results of displacement were expressed in millimeters (mm).

Statistics

Statistical analysis was performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). Doses and volumes in FB and DIBH were compared for statistically significant differences using a 2-sided paired t-test. Welch's two sample t-test was used to compare the entry-to-exit time in DIBH and Right-FB. The threshold for statistical significance was set at $P < 0.05$.

Results

Patients

Sixty-four patients with left-sided early-stage breast cancer who were enrolled and received DIBH radiotherapy in our institution were eligible for this study. Table 1 shows the patients' characteristics. All patients received breast-conserving surgery and consecutive DIBH-RT with 42.56 Gy in 16 fractions. The average age of the patients was 52 (47–59) years, and their average height, weight, and body mass index (BMI) were 156.2 (154–160) cm, 53 (47–59.7) kg, and 21.9 (19.9–23.8) kg/m^2, respectively. The quadrant distribution of primary lesions included an upper-outer area of 34 patients, upper-inner area of 13 patients, lower-outer area of 14 patients, lower-inner area of 4 patients, and central area or nipple of 2 patients. Three patients had lesions on the lower-outer and upper-outer boundaries, which were counted in both areas.

Table 1. Patient characteristics

Characteristics	Median	Range (IQR)
Age	52	32–74 (47–59)
Height (cm)	156.2	145–165.3 (154–160)
Weight (kg)	53	39–79.6 (47–59.7)
BMI (kg/m^2)	21.9	16.7–30.1 (19.9–23.8)
Quadrants		
Upper-outer	34	
Upper-inner	13	
Lower-outer	14	
Lower-inner	4	
Central portion, nipple	2	

Three patients with lower-outer and lower-inner lesions were counted in both quadrants. BMI, body mass index; IQR, interquartile range

Setup reproductivity assessment

A total of 30 patients were evaluated. Figures 3a-d show the histograms of inter- and intra-fractional displacement in X and Y directions. The inter-fractional displacement of D_{X_inter}, D_{Y_inter}, and D_{2D_inter} were -0.07 ± 1.69, 1.02 ± 2.09, and 2.32 ± 1.30, respectively. The intra-fractional displacement of D_{X_intra}, D_{Y_intra}, and D_{2D_intra} were -0.14 ± 0.57, -0.06 ± 0.36, and 0.55 ± 0.43, respectively. The D_{2D_ALL} was 2.46 ± 1.24, and the calculated D_{2D_ALL} + 2SD was 4.94 mm. The results showed that our setup margin (5 mm) satisfied the required margin.

Treatment time

The entry-to-exit time of 64 DIBH-RT patients and 44 right breast cancer patients treated in FB (Right-FB) were recorded. Figure 4 shows the summary of the entry-to-exit time for each fraction. The median (IQR) time in DIBH and Right-FB were as follows: all fractions, 9 (8-11) minutes in DIBH and 7 (6-9) minutes in Right-FB ($P = 3.95e^{-23}$); first fractions, 22 (19-27) minutes in DIBH and 16 (13-25) minutes in Right-FB ($P = 0.0083$); and 2-16 fractions, 9 (8-11) minutes in DIBH and 7 (6-8) minutes in Right-FB ($P = 1.39e^{-50}$).

The mean MU per fraction was 307 (SD 11.3, IQR 301-312), and the beam-on time for a dose rate of 600 MU/minutes was approximately 30 seconds.

Plan comparison

We compared the volumes and doses of all contours in FB and DIBH plans. The median (IQR) volumes (mL) of all contours were as follows: CTV, 230 (149-283) in FB and 232 (160-287) in DIBH (P = 0.43); HEART, 545 (484-599) in FB and 547 (479-594) in DIBH (P = 0.31); LAD, 1.98 (1.64-2.47) in FB and 2.05 (1.71-2.45) in DIBH (P = 0.24); LUNG, 2325 (2022-2577) in FB and 3670 (3245-3960) in DIBH (P = $2.77e^{-29}$). There was a significant volume increase in DIBH for LUNG, but the other contours were not significantly different between FB and DIBH.

The median (IQR) doses of all contours (Gy) were as follows: CTV_D95, 41.0 (40.6–41.4) in FB and 41.9 (40.7–41.5) in DIBH (P = 0.33); CTV_D50, 42.9 (42.6–43.1) in FB and 42.9 (42.6–43.1) in DIBH (P = 0.30); HEART mean dose, 1.67 (1.10–2.45) in FB and 0.71 (0.59–0.81) in DIBH (P = $9.72e^{-15}$); LAD mean dose, 13.0 (5.1–17.7) in FB and 2.31 (1.79–3.22) in DIBH (P = $6.65e^{-15}$); LUNG mean dose, 2.42 (2.04–3.00) in FB and 2.03 (1.72–2.42) in DIBH (P = $6.80e^{-8}$). The LUNG_V20 was 4.64 (3.72–5.83) (%) in FB and 3.71 (2.94–4.48) (%) in DIBH (P = $1.05e^{-9}$). There was a significant dose reduction in DIBH for HEART, LAD, and LUNG mean doses, while CTV_D95 and CTV_D50 doses between FB and DIBH settings were not statistically different. The dose differences between FB and DIBH settings are summarized in Table 2.

Table 2. Summary of the comparison between the FB and DIBH plans

Contour volume (mL)	FB plan Median value (IQR)	DIBH plan Median value (IQR)	P value
CTV	230 (149–283)	232 (160–287)	.432
HEART	545 (484–599)	547 (479–594)	.311
LAD	1.98 (1.64–2.47)	2.05 (1.71–2.45)	.243
LUNG	2325 (2022–2577)	3670 (3245–3960)	2.77e^-29*
Contour dose			
CTV_D95 (Gy)	41.0 (40.6–41.4)	41.9 (40.7–41.5)	.333
CTV_D50 (Gy)	42.9 (42.6–43.1)	42.9 (42.6–43.1)	.302
HEART mean dose (Gy)	1.67 (1.10–2.45)	0.71 (0.59–0.81)	9.72e^-15*
LAD mean dose (Gy)	13.0 (5.1–17.7)	2.31 (1.79–3.22)	6.65e^-15*
LUNG mean dose (Gy)	2.42 (2.04–3.00)	2.03 (1.72–2.42)	6.80e^-8*
LUNG_V20 (%)	4.64 (3.72–5.83)	3.71 (2.94–4.48)	1.05e^-9*

CTV, clinical target volume; CTV_D50, the dose of 50% of CTV volume received; CTV_D95, the dose of 95% of CTV volume received; DIBH, deep inspiration breath-holding; FB, free-breathing; IQR, interquartile

range; LAD, left anterior descending artery; LUNG_V20, the percent volume of LUNG receiving 20 Gy or more. * indicates a significant difference ($p < 0.05$, 2-sided paired *t*-test)

Discussion

In this study, we showed that our DIBH-RT technique was effective for dose reduction while achieving the required accuracy. Our method had some strong advantages. First, no expensive devices were needed for tracking the surface motion or respiratory cycle. Our method required only a room camera for tracking a patient's surface motion and used manual irradiation after the laser was aligned with the DIBH mark. Since the procedure is simple and there is no additional cost, it can be easily implemented in new facilities. Second, the treatment time was short when using the DIBH-RT method. Technically, it requires a substantial amount of time to guide the patient's breathing and to adjust and fit the monitoring devices. However, our method required minimal patient training because the irradiation was performed according to the original breathing of each patient, and trained radiologists appropriately judged the deviation of breathing and interrupted the irradiation. Further, it took approximately 24 minutes for the first irradiation and approximately 10 minutes for the second and subsequent irradiations. Although our DIBH technique required an additional 6 minutes for the first irradiation and 2 minutes for each subsequent irradiation compared with FB treatment, no resultant change in patient throughput was required in our method. Third, our method used the EPID and DRR images to monitor intra-fractional 2D displacement. There is uncertainty regarding the internal alignment using only body surface monitors, but our method can acquire internal information during irradiation in real time.

We conducted our study in three main phases. In the first phase, we checked the inter-fractional and intra-fractional displacement in 30 selected patients. The average inter-fractional motion was 2.32 ± 1.30 mm, and the average intra-fractional motion was 0.55 ± 0.43 mm. The intra-fractional motion was minimized by real-time verification using cine-EPID and DRR images. The result of the total displacement was 2.46 ± 1.24 mm, and our setup margin of 5 mm was satisfied with a mean + 2SD of total displacement (4.94 mm).

The second phase of the study consisted of examining the irradiation time in all analyzed patients. We measured the beam-on time as well as the entry-to-exit time, which is the total time it takes for the patient to enter and exit the treatment room. Most of the literature on DIBH does not mention the time required for irradiation, but it should be published because DIBH takes longer to set up than FB irradiation [19, 21, 26]. Further, repeated deep breath-holds during daily treatments may increase the psychological and physical burden on the patient; however, this has never been reported. With our method, for 4 deep breath-holds (10 to 15 seconds for each beam) per irradiation, the median beam-on time was 0.51 minutes, and the entry-to-exit time was approximately 9 minutes, except for the first irradiation. It requires only 2 minutes more than FB irradiation. Bartlett et al. reported that the mean total time of DIBH-RT was 19 minutes [16]. Lee et al. reported that the mean total time of FB and DIBH-RT were 5.3 minutes and 10.5 minutes, respectively [26]. Although there are few reports for comparison, we believe that the increase in patient burden associated with our DIBH-RT technique may be minimal compared with that with non-DIBH-RT.

In the last phase of this study, we compared the dose metrics of FB and DIBH plans in all the patients. The volumes of all contours in both plans were not statistically different except that of deeply inhaled lungs. The doses of CTV (both D95 and D50) were not statistically different, but the doses of all OARs, including the mean heart dose, could be reduced in the DIBH treatment plan. According to some reports, reducing the average dose to the heart is effective in reducing severe late cardiovascular disease [7, 10, 12, 13]. Darby et al. reported that the mean heart dose was strongly related to major coronary events, with no apparent threshold [10]. Further, Taylor et al., in their systematic literature review, showed an increase in the excess rate ratios for cardiac mortality of 0.04 per Gy mean heart dose [12]. Differing from these reports, in our study, FB treatment plans also had low average mean doses, possibly because the planners were aware of past reports and more conscious of avoiding cardiac doses from the outset. Several studies have reported on dose reduction with DIBH compared with FB [17, 26, 27]. In these studies, DIBH-RT was performed using RPM, AlignRT, or Abchess [28]. Our study showed that dose reduction could be obtained to a similar degree without using such devices.

Our study has some important limitations. First, this study is a retrospective, single-institution study. Second, fractional displacement was evaluated in 2 dimensions and measured manually so that a detailed quantitative evaluation of 0.1 mm or less could not be done. Third, our DIBH method was not directly compared with conventional device using DIBH. Therefore, it is necessary to verify at other institutions or to compare our method and conventional DIBH using crossovers in the same patients.

Conclusions

As only minor inter-fractional and intra-fractional displacement were observed, this simple and cost-effective DIBH technique could ensure a feasible method of voluntary DIBH irradiation. It could reduce the radiation doses to the heart, LAD, and lungs significantly while maintaining CTV coverage compared with the FB technique. As a future prospect of this study, we will verify our new technique at other institutions and widely implement it in clinical settings.

List Of Abbreviations

BMI: body mass index

CT: computed tomography

CTV: clinical target volume

DIBH: deep inspiration breath-hold

DIBH-RT: DIBH radiotherapy

DRR: digitally reconstructed radiography

FB: free-breathing

IQR: interquartile range

ITV: internal target volume

LAD: left anterior descending artery

MU: monitor units

OARs: organs at risk

PTV: planning target volume

Right-FB: FB radiotherapy

RPM: real-time position management

Declarations

Ethics approval and consent to participate

The Institutional Review Board (IRB) of Aichi Cancer Center Hospital approved our study (approve number: 2019-1-211).

Consent for publication

Not applicable.

Availability of data and materials

Owing to data privacy policy at our facility, publication of patient-related raw is not possible.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Tomoki Kitagawa analyzed the data. Takahiro Aoyama, Hidetoshi Shimizu, Kohei Wakabayashi, Risei Miyauchi collected the data. Hiroshi Tanaka, Hiroyuki Tachibana, and Takeshi Kodaira interpreted the data and supervised the study. All authors reviewed and approved the final manuscript.

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Figures

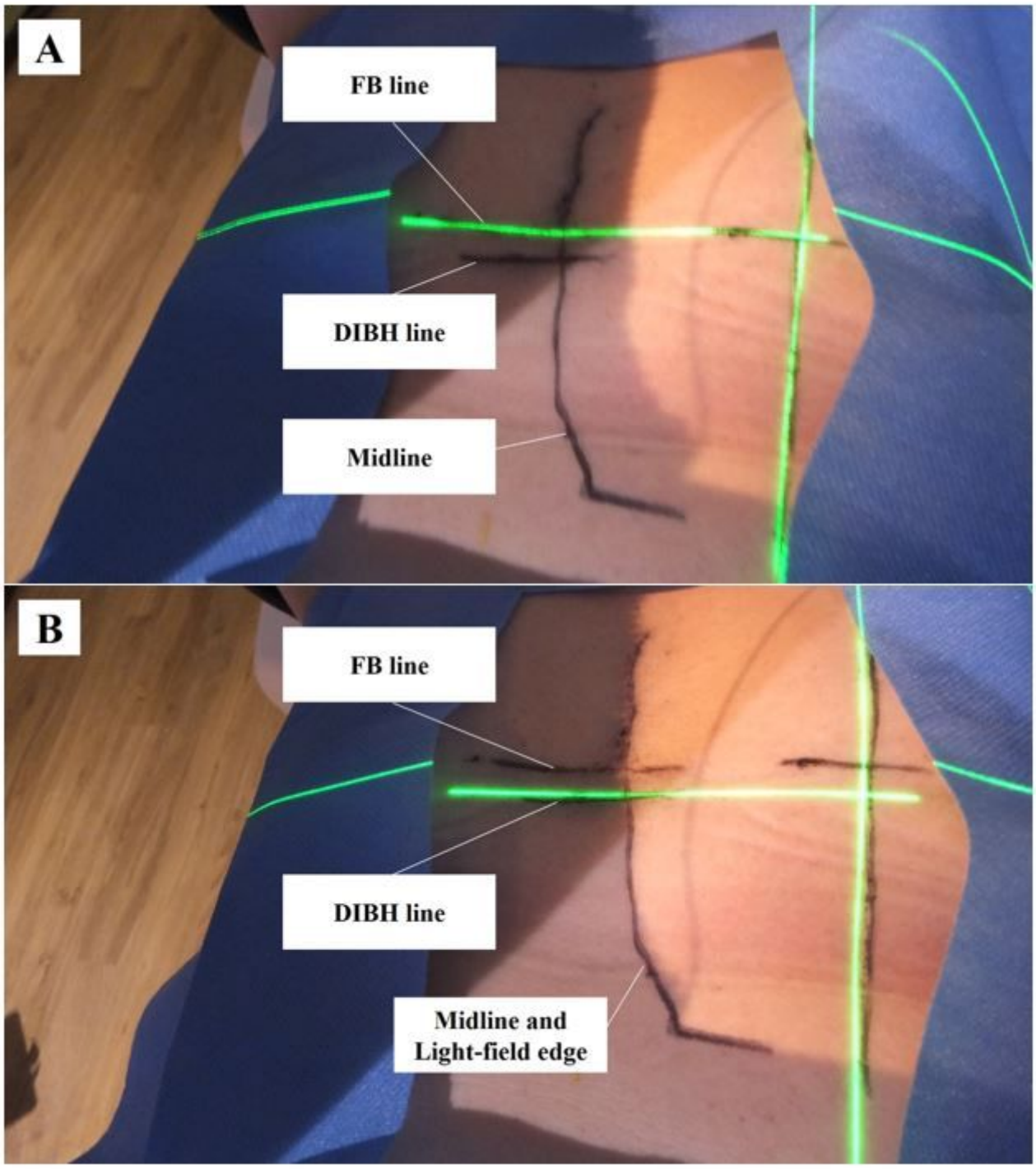

Figure 1

Daily setup before the irradiation. The patient is initially setup so that the laser aligns with the FB line (A) and instructed to take a deep breath-hold so that the laser now aligns with the DIBH line and the light-field edge aligns with the midline (B). DIBH, deep inspiration breath-holding; FB, free-breathing

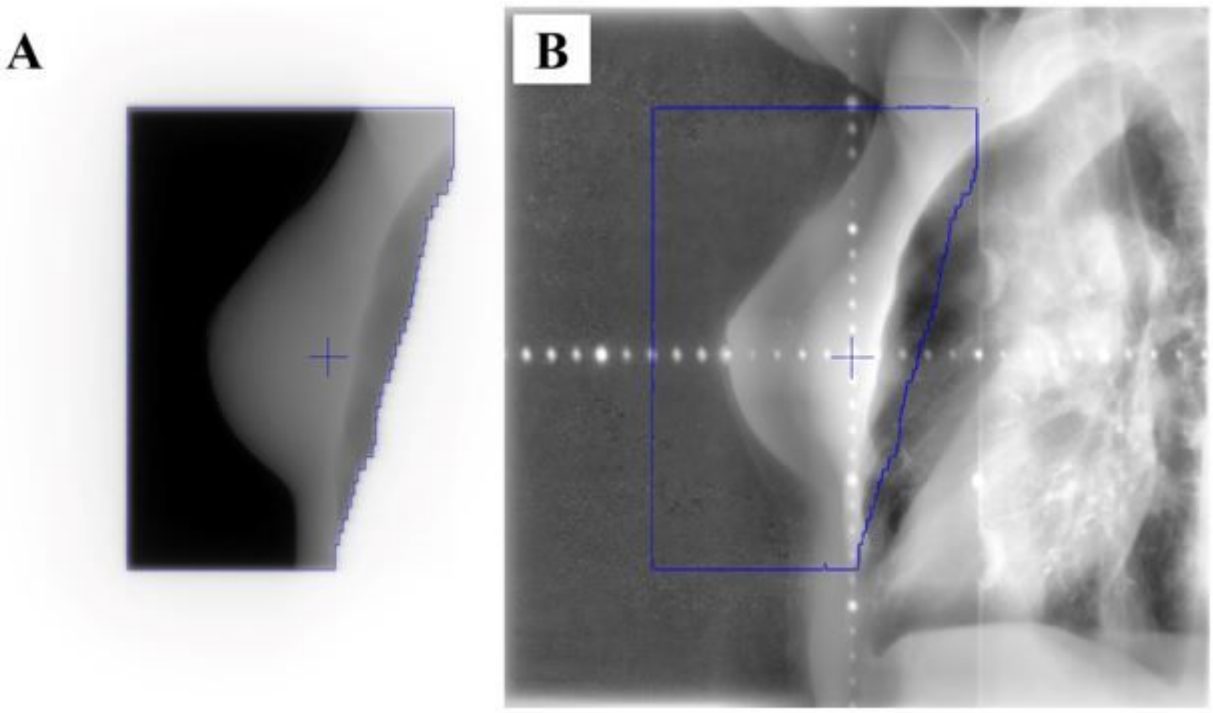

Figure 2

Daily setup during the irradiation. During the irradiation, cine images on an electronic portal imaging device (A) and a digitally reconstructed radiography image (B) were placed side by side and matched on-line in real time to minimize the isocenter positioning errors.

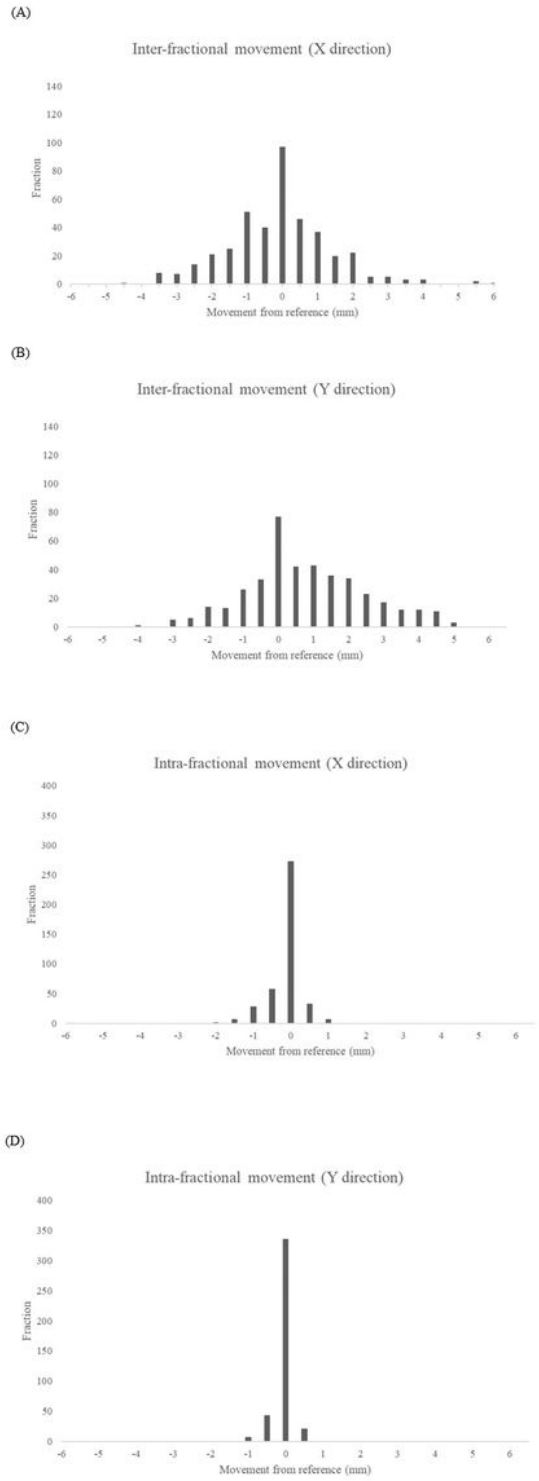

Figure 3

The results of setup verification for the selected 10 patients. Inter-fractional displacement in (A) X (anterior–posterior) direction and (B) Y (cranio–caudal) direction. Intra-fractional displacement in (C) X direction and (D) Y direction. Fr: fraction, SD: standard deviation

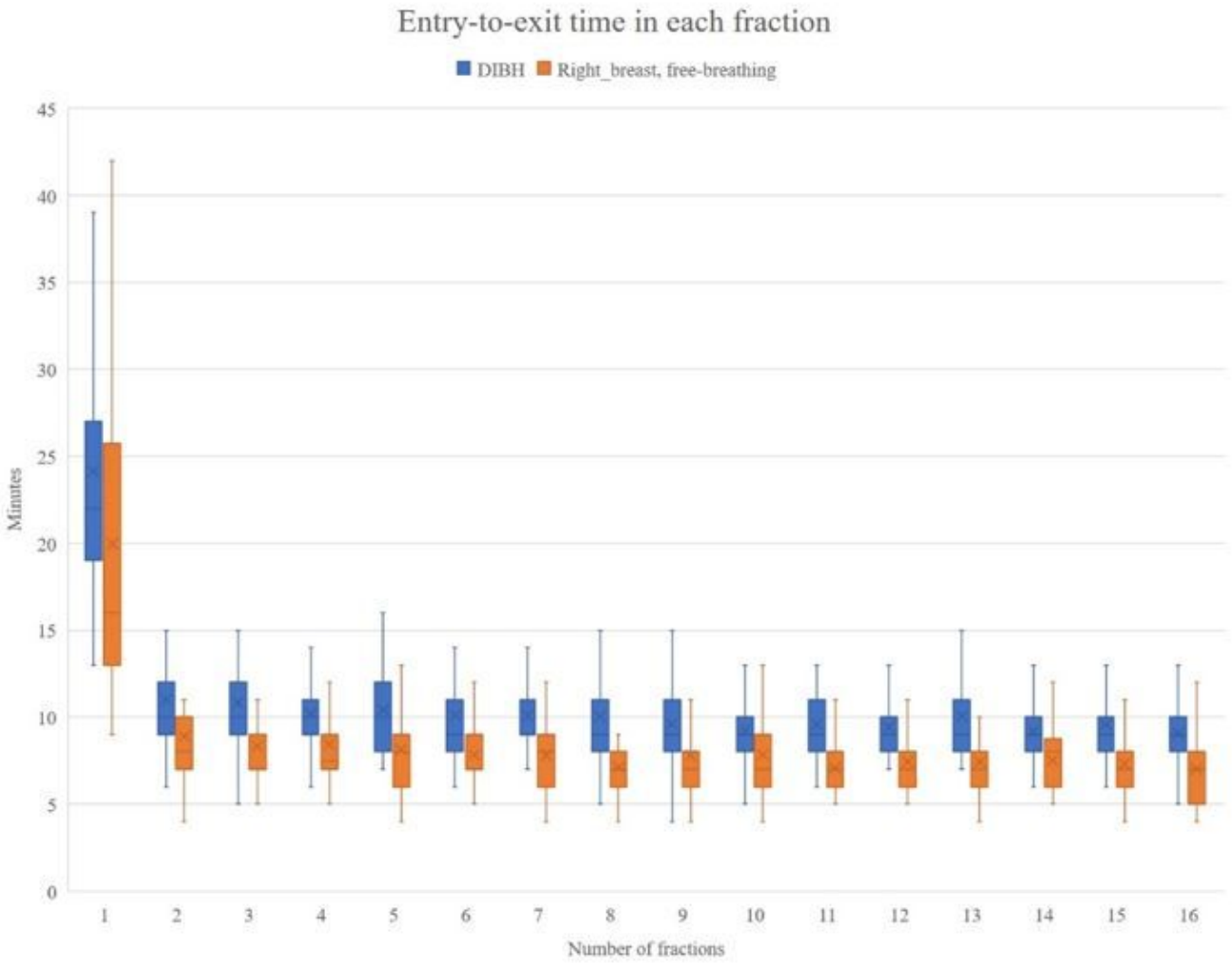

Figure 4

Box plot showing the entry-to-exit time for each fraction. For each fraction, the entry-to-exit time was measured from when a patient entered the treatment room to when she exited.