

Dosimetric evaluation of deep inspiration breath hold for left-sided breast cancer: analysis of patient-specific parameters related to heart dose reduction

Ryohei Yamauchi^{1,2,*}, Norifumi Mizuno¹, Tomoko Itazawa¹, Hidetoshi Saitoh²
and Jiro Kawamori¹

¹Department of Radiation Oncology, St Luke's International Hospital, Tokyo, Japan

²Graduate School of Human Health Sciences, Tokyo Metropolitan University, Tokyo, Japan

*Corresponding author. Department of Radiation Oncology, St Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo, 104-8560, Japan. Email: yamauchi.ryouhei@gmail.com TEL: +81-3-3541-5151; FAX: +81-3-3544-0649;

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ABSTRACT

Deep inspiration breath hold (DIBH) is a common method used worldwide for reducing the radiation dose to the heart. However, few studies have reported on the relationship between dose reduction and patient-specific parameters. The aim of this study was to compare the reductions of heart dose and volume using DIBH with the dose/volume of free breathing (FB) for patients with left-sided breast cancer and to analyse patient-specific dose reduction parameters. A total of 85 Asian patients who underwent whole-breast radiotherapy after breast-conserving surgery were recruited. Treatment plans for FB and DIBH were retrospectively generated by using an automated breast planning tool with a two-field tangential intensity-modulated radiation therapy technique. The prescribed dose was 50 Gy in 25 fractions. The dosimetric parameters (e.g., mean dose and maximum dose) in heart and lung were extracted from the dose-volume histogram. The relationships between dose-volume data and patient-specific parameters, such as age, body mass index (BMI), and inspiratory volume, were analyzed. The mean heart doses for the FB and DIBH plans were 1.56 Gy and 0.75 Gy, respectively, a relative reduction of 47%. There were significant differences in all heart dosimetric parameters ($p < 0.001$). For patients with a high heart dose in the FB plan, a relative reduction of the mean heart dose correlated with inspiratory volume ($r = 0.646$). There was correlation between the relative reduction of mean heart dose and BMI ($r = -0.248$). We recommend considering the possible feasibility of DIBH in low BMI patients because the degree of benefit from DIBH varied with BMI.

Keywords: breast cancer; deep inspiration breath hold (DIBH); heart dose; respiratory motion management

INTRODUCTION

Breast cancer is the most common cancer in women, with an estimated worldwide incidence of 2.1 million cases (24.2%) in 2018 [1]. Adjuvant radiation therapy is commonly used in breast cancer to reduce the risk of local recurrence and breast-cancer-specific mortality [2–4]. As is well known, several studies have reported that incidental exposure of the heart to radiation increases the risk of radiation-induced cardiac toxicity [5–7]. Darby *et al.* showed that the rate of major acute coronary events increased linearly with the mean heart dose (MHD) by 7.4% per gray [8]. van den Bogaard *et al.* reported a similar result for a study

of an independent cohort of consecutive patients, using modern radiation techniques and fractionation schemes [9]. Cardiac damage from radiation therapy has been found to be amplified in patients who have received anthracycline-based chemotherapy and trastuzumab [10].

Deep inspiration breath hold (DIBH) is a method for reducing heart dose and is commonly used worldwide. This technique displaces the heart away from the chest wall and minimizes cardiac exposure in the treatment field. There are several methods for performing DIBH, such as active breath control, external infrared box marker, or optical surface monitor [11]. Dosimetric studies have shown that DIBH for

left-sided breast cancer patients can reduce the heart dose [12–15]. The reports of dosimetric evaluation of DIBH have mostly come from Europe and North America, and the population sizes were mainly from 10 to 30 patients. The degree of benefit from DIBH may vary with patient characteristics. Therefore, the heart dose reduction may be affected by difference in the physique or anatomical variation of chest shape. When BMI was used as one of the physique indexes, the age-standardized mean BMI and proportion of overweight Japanese women were 22.6 kg/m² and 19.0%, respectively [16]. On the other hand, the Non-communicable Disease (NCD) Risk Factor Collaboration reported that the mean BMIs in Europe and North America were larger than that of Eastern Asia [17]. Furthermore, the inspiratory volume during DIBH directly involved displacement of the heart, which can affect the heart dose. However, few papers have reported the relationship between dose reduction and patient-specific parameters.

Dosimetric evaluation of DIBH requires generating a treatment plan for free breath computed tomography (FB-CT) and DIBH-CT to compare the dose to various targets. In this process, parameters of a treatment plan, such as the dose distribution, gantry angle, and segment shape, are determined by the planner (e.g. a physician, medical physicist, or dosimetrist). In this study, an automated planning system was used to reduce this potential uncertainty.

The aim of this study was to quantify the dose reduction to the heart when using DIBH-CT rather than FB-CT for Asian patients in a larger population, compare the results with those of previous reports, and to investigate the patient-specific parameters related to heart dose reduction.

METHODS AND MATERIALS

Patient selection

A total of 85 patients with left-sided breast cancer treated at our institution from June 2016 to January 2019 were recruited. The study protocol was approved by our Institutional Review Board. The analysis performed for this study consisted of purely dosimetric modeling and was fully independent of the care delivered to each patient. The patients received whole-breast irradiation after breast-conserving surgery (BCS), not including regional lymph node irradiation. All patients underwent whole-breast irradiation using medial and lateral tangential intensity-modulated radiation therapy (IMRT).

Patients with left-sided breast cancer who were able to breath hold at approximately 70% to 80% of the maximal inspiratory capacity for ≥ 30 s were considered. The criterion of minimal breath hold time was set to 20 s.

CT simulation for DIBH

The patients received DIBH information at their radiation oncology consultation prior to the CT simulation. In addition, they were instructed to practice breath-hold training several times a day from ≥ 1 week before the day of CT simulation.

CT simulation and treatment were performed with the patient in the supine position with both arms raised above the head via wing-support immobilization (Engineering System Co., Ltd, Matsumoto, Nagano, Japan). CT simulations during FB and DIBH were performed by using the GE LightSpeed RT16 CT scanner (GE Healthcare, Waukesha, WI, USA). Four radio-opaque markers and a radio-opaque

wire were placed on the patient as recommended by RaySearch Laboratories and described in the RayStation user manual [18]. DIBH-CT was performed continuously after FB-CT without moving the position of these markers and wire.

The Varian real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) was used to track respiratory motion. The RPM infrared box marker was placed on the patient's right breast so that it did not interrupt the paths of tangential beams. To establish a reproducible and stable breathing amplitude during DIBH, each patient performed breathing training with the RPM system and a visual feedback system prior to the CT scan. The vertical displacements of the chest wall due to respiratory movement during FB and DIBH were measured from the RPM wave signal and compared.

Automated breast planning

Tangential breast step-and-shoot IMRT plans were generated on FB-CT and DIBH-CT by using a radiation treatment system (RayStation, version 4.7 or 6.2; RaySearch Laboratories, Stockholm, Sweden). The automated breast planning tool implemented in RayStation provided contouring of all relevant target and risk organs; set-up of beams, including heuristic optimization of gantry and collimator angles; and optimization. Previous studies have reported the utility of automated planning and clinical implementation for breast cancer radiation therapy [19, 20]. In this study, we used a new commercial automated planning tool for tangential breast IMRT that had been developed on the basis of these reports.

The tangential IMRT in this automated planning tool is a similar to 'Hybrid IMRT', and it is comprised of two opposed tangential open beams, along with two to five IMRT beams set at the same angles. The weight of the open beams and the inversely optimized IMRT beams were 80% and 20%, respectively [19, 21]. Therefore, it can provide good robustness against uncertainty comparable with conventional radiotherapy [19–22]. Note that the IMRT modulation was used to improve dose homogeneity in the target and was not used for dose reduction of OARs.

The automated algorithm of gantry and collimator angle optimization introduces treatment beams corresponding to the anatomical points, such that the beams pass through the medial and lateral points. The radiation field parameters such as jaw opening, gantry angle, and collimator angle, were generated on the basis of the radio-opaque markers and the wire. Therefore, treatment plans that have equivalent dose distributions can be generated from FB-CT and DIBH-CT. Figure 1 shows the dose distribution, beam's eye view, radiation field on the patient's surface, and fusion images for the FB and DIBH plans.

The automatic segmentation is performed for the relevant target and organs at risk (e.g. breast, lung and heart). Clinical target volume (abbreviated as aCTV in this tool) for whole-breast irradiation was automatically generated by an automated algorithm. The aCTV is defined as the volume of tissue irradiated by the initial beam at the 55% isodose level, excluding OARs and contracted by the skin surface and 10 mm in the superior–inferior direction. The validity of this target delineation was considered in advance [21]. The organs at risk were re-delineated by a single medical physicist, if needed. These definitions of structures are in accord with the Radiation Therapy Oncology Group Breast cancer atlas [23].

Table 1. Patient characteristics

Parameter		n = 85
Age (years old)	Mean ± 1SD [range]	49.3 ± 9.1 [28–70]
Height (m)	Mean ± 1SD	1.58 ± 0.05
Weight (kg)	Mean ± 1SD	54.7 ± 9.4
BMI (kg/m ²)	Mean ± 1SD	21.9 ± 3.7
BMI categories	< 18.5	14 (16.5%)
	18.5, < 25.0	57 (67.1%)
	25.0, < 30.0	10 (11.8%)
	≥ 30.0	4 (4.7%)
Tumor site	Inner-upper (A)	19 (22.4%)
	Inner-lower (B)	17 (20.0%)
	Outer-upper (C)	31 (36.5%)
	Outer-lower (D)	16 (18.8%)
	Center (E)	2 (2.4%)
Chest wall displacement (cm)	Mean ± 1SD [range]	1.3 ± 0.4 [0.5–2.0]

SD = standard deviation, BMI = body mass index.

Table 2. The target and organs volume for FB-CT and DIBH-CT

Target/organs	FB	DIBH	Difference (DIBH – FB, DIBH/FB)	
	Mean ± 1SD (cm ³) (Range)	Mean ± 1SD (cm ³) (Range)	Absolute Mean ± 1SD (cm ³)	Ratio Mean ± 1SD
aCTV	417.0 ± 228.5 (36.5–1176.7)	408.2 ± 224.1 (36.0–1084.9)	–8.8 ± 23.3	0.98 ± 0.05
Heart	507.8 ± 85.7 (326.9–727.1)	487.1 ± 80.6 (317.5–683.6)	–20.8 ± 48.7	0.96 ± 0.09
Lung (right)	1139.9 ± 234.6 (601.6–1772.0)	1841.3 ± 304.8 (1098.2–2490.9)	701.4 ± 222.2	1.64 ± 0.27
Lung (left)	1395.9 ± 241.6 (861.5–2022.7)	2132.0 ± 337.6 (1314.5–2908.0)	736.1 ± 249.2	1.54 ± 0.22
Lungs	2535.2 ± 464.0 (1463.63–3794.6)	3971.8 ± 626.1 (2444.1–5398.0)	1436.6 ± 463.5	1.58 ± 0.24

CTV = clinical target volume, SD = standard deviation, FB = free breath, DIBH = deep inspiration breath hold.

Dose calculation was performed by using a collapsed-cone convolution algorithm with heterogeneity correction and a constant 2 mm calculation grid size. The prescribed dose was 50 Gy in 25 fractions. The dose was normalized to the average dose of aCTV. All plans were generated retrospectively, and a 6 MV X-ray linear accelerator (Clinac-iX; Varian Medical Systems) was used.

Dosimetric comparison

Dose–volume data regarding the mean dose (D_{mean}) to the heart and lung (including right and left lung), percentage and absolute volume of organs receiving a dose greater than X Gy ($V_{X Gy}$) (where X Gy is from 5 Gy to 25 Gy), and dose to the highest irradiated 2 cm³ and 0.1 cm³ volumes ($D_{2 cm^3}$ and $D_{0.1 cm^3}$) of the irradiated volume were recorded. The following patient-specific parameters were collected; age, height, weight, body mass index (BMI), tumor site, chest wall displacement between FB and DIBH, and the inspiratory volume during DIBH. The inspiratory volume during DIBH was calculated from lung volume difference between FB and DIBH. DIBH and FB treatment plans using predetermined dosimetric parameters for organs for each patient were compared. Relative reduction of heart and lung dose parameter for each individual patient was calculated by the absolute difference between FB and DIBH divided by the value of FB. The relationships and

correlations between dose reduction and patient-specific parameters were investigated.

Statistical analysis

All statistical analyses were performed by using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [24]. The paired *t*-test and analysis of variance were used for group comparisons as required. The Pearson correlation coefficient was used for correlational analysis. The predictor factors that affected dose reduction of heart were examined using univariable and multivariable analyses (multiple regression analysis). The variance inflation factor (VIF) was used to verify multicollinearity (the maximum acceptable level of VIF was set to 5). In this study, $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Between June 2016 and January 2019, a total of 85 Asian patients (Japanese: 83 patients, Chinese: 2 patients) who received radiation therapy with DIBH were recruited. The characteristics of all patients

Table 3. Dosimetric and volume comparison between FB and DIBH plans for all patients

	FB plan	DIBH plan	Absolute difference	Relative reduction (%)	P-value
	Mean ± 1SD	Mean ± 1SD	Mean ± 1SD	Mean ± 1SD	
Heart					
Mean dose (cGy)	156.2 ± 94.0	75.2 ± 39.9	80.9 ± 68.9	46.9 ± 14.1	<0.001
V _{5 Gy} (%)	3.1 ± 2.7	0.7 ± 1.2	2.4 ± 2.0	86.8 ± 16.3	<0.001
V _{10 Gy} (%)	1.9 ± 2.2	0.3 ± 0.8	1.6 ± 1.7	92.5 ± 13.5	<0.001
V _{15 Gy} (%)	1.6 ± 2.0	0.2 ± 0.7	1.4 ± 1.6	93.9 ± 12.8	<0.001
V _{20 Gy} (%)	1.4 ± 1.8	0.2 ± 0.6	1.2 ± 1.5	94.7 ± 12.2	<0.001
V _{25 Gy} (%)	1.3 ± 1.7	0.2 ± 0.6	1.1 ± 1.4	95.3 ± 11.9	<0.001
V _{5 Gy} (cm ³)	15.7 ± 14.2	3.1 ± 5.6	12.5 ± 10.9	87.1 ± 16.1	<0.001
V _{10 Gy} (cm ³)	9.6 ± 11.1	1.4 ± 3.7	8.2 ± 9.2	92.7 ± 13.5	<0.001
V _{15 Gy} (cm ³)	8.1 ± 10.1	1.1 ± 3.2	7.0 ± 8.6	94.0 ± 12.9	<0.001
V _{20 Gy} (cm ³)	7.2 ± 9.4	0.9 ± 2.9	6.3 ± 8.1	94.8 ± 12.0	<0.001
V _{25 Gy} (cm ³)	6.6 ± 8.9	0.8 ± 2.7	5.9 ± 7.8	95.5 ± 11.4	<0.001
D _{2 cm³} (cGy)	2860.7 ± 1738.0	840.8 ± 1137.4	2019.9 ± 1499.0	68.0 ± 23.8	<0.001
D _{0.1 cm³} (cGy)	3989.8 ± 1343.3	1640.0 ± 1585.5	2349.8 ± 1460.9	60.4 ± 31.1	<0.001
Lung (right)					
Mean dose (cGy)	12.0 ± 2.8	12.8 ± 2.4	-0.8 ± 2.3	-10.3 ± 23.8	0.001
D _{2 cm³} (cGy)	94.4 ± 29.8	109.9 ± 35.9	-15.6 ± 19.9	-18.5 ± 21.2	<0.001
Lung (left)					
Mean dose (cGy)	566.3 ± 232.2	513.1 ± 195.7	53.3 ± 85.6	6.9 ± 14.9	<0.001
V _{5 Gy} (%)	18.1 ± 6.5	17.7 ± 5.9	0.3 ± 2.5	-1.6 ± 20.7	0.225
V _{20 Gy} (%)	10.4 ± 5.2	9.2 ± 4.4	1.2 ± 1.9	2.3 ± 55.2	<0.001
Lungs					
Mean dose (cGy)	260.6 ± 105.2	244.9 ± 92.0	15.7 ± 39.3	3.3 ± 15.7	<0.001
V _{5 Gy} (%)	8.1 ± 3.0	8.2 ± 2.8	-0.1 ± 1.2	-5.1 ± 22.0	0.354
V _{20 Gy} (%)	4.7 ± 2.3	4.3 ± 2.0	0.4 ± 0.8	0.0 ± 59.2	<0.001

FB = free breath, DIBH = deep inspiration breath hold.

are summarized in Table 1. The mean age of the patients was 49.3 years (range, 28–70). BMI was classified according to World Health Organization categories as ‘Underweight’ (<18.5 kg/m²), ‘Normal weight’ (18.5 kg/m² to <25.0 kg/m²), ‘Pre-obesity’ (25.0 kg/m² to <30.0 kg/m²) and ‘Obesity’ (>30.0 kg/m²). Obesity is further classified from Class I to Class III [25]. The mean BMI in this study was 21.9 kg/m² (range, 14.2–36.1 kg/m²), and most patients were included in the category of ‘Underweight’ or ‘Normal weight.’ The mean chest wall displacement in the anterior–posterior direction by DIBH was 1.3 cm.

Target and organ volumes

Table 2 shows the differences in target and organ volumes between FB-CT and DIBH-CT. The target and heart volumes were comparable between FB- and DIBH-CT. The mean inspiratory volume during DIBH was 1436.6 cm³, and the mean volume of the lungs during DIBH increased by ~160% relative to that during FB. There was a weak correlation between chest wall displacement and inspiratory volume during DIBH ($r = 0.321$): the greater the chest wall position displaced by chest breathing, the greater the inspiratory volume, except for two patients.

Dosimetric comparison

Table 3 shows dose–volume data for organs at risk for the FB plans and DIBH plans. The dosimetric evaluation showed that the MHD was 156.2 cGy in the FB plans and 75.2 cGy in the DIBH plans ($P < 0.001$), wherein the absolute difference was 80.9 cGy and the relative reduction was 46.9%. In almost all measured data for the heart, the dose–volume data for the DIBH plans were reduced relative to the data for the FB plans. In only one case with a $D_{0.1 \text{ cm}^3}$ of the heart (Patient 6), was the maximum heart dose for the FB plan (4993 cGy) lower than that for the DIBH plan (4997 cGy). The mean heart $V_{25 \text{ Gy}}$ (%) decreased from 1.3% to 0.2%, which was a relative decrease of 95.3% ($P < 0.001$). Of the 85 patients, the heart was spared completely from the radiation field by DIBH in 57 patients. The mean lungs dose was reduced from 260.6 cGy to 244.9 cGy, and the mean lungs $V_{25 \text{ Gy}}$ (%) was reduced from 4.7% to 4.3% ($P < 0.001$). There was no dosimetric benefit for mean or maximum dose in the right lung. Figure 2A and B show the mean heart dose difference (MHDD) and the relative reduction of mean heart dose (rrMHD) between FB and DIBH against MHD for FB. There was a significant correlation between the MHDD or rrMHD and MHD for FB (MHDD: $r = 0.926$, $P < 0.001$; rrMHD: $r = 0.585$, $P < 0.001$).

Table 4. Univariable analysis of predictors of absolute and relative reduction of mean heart dose

Variables	MHDD		rrMHD	
	<i>r</i> (95% CI)	<i>P</i> -value	<i>r</i> (95% CI)	<i>P</i> -value
Age	−0.016 (−0.228–0.198)	0.887	−0.033 (−0.244–0.182)	0.768
BMI	−0.204 (−0.400–0.009)	0.061	−0.248 (−0.438 –0.037)	0.022
Lung volume difference	0.094 (−0.122–0.301)	0.393	0.169 (−0.045–0.369)	0.121
Ratio of lung volume	0.175 (−0.040–0.374)	0.110	0.206 (−0.008–0.401)	0.059
Volume of aCTV	−0.135 (−0.338–0.081)	0.219	−0.195 (−0.392–0.019)	0.074
Volume of heart	0.057 (−0.158–0.267)	0.602	0.052 (−0.163–0.262)	0.635
Chest-wall displacement	0.299 (0.092–0.481)	0.005	0.306 (0.099–0.487)	0.004
	(Mean ± 1SD)		(Mean ± 1SD)	
BMI categories				
< 18.5	74.4 ± 58.4	0.341	0.47 ± 0.13	0.147
18.5, < 25.0	89.1 ± 74.8		0.49 ± 0.14	
25.0, < 30.0	60.7 ± 52.4		0.41 ± 0.16	
≥ 30.0	37.5 ± 10.4		0.36 ± 0.06	
Tumor site				
Inner-upper (A)	80.7 ± 91.2	0.854	0.45 ± 0.14	0.846
Inner-lower (B)	90.0 ± 54.8		0.47 ± 0.14	
Outer-upper (C)	70.4 ± 55.8		0.47 ± 0.15	
Outer-lower (D)	91.4 ± 81.8		0.49 ± 0.14	
Center (E)	84.0 ± 33.9		0.55 ± 0.05	

MHDD = mean heart dose difference, rrMHD = relative reduction of mean heart dose, SD = standard deviation, BMI = body mass index, aCTV = automated clinical target volume, *r* = correlation coefficient, CI = confidence interval.

Relationship between patient-specific parameters and dose–volume data

Table 4 shows the univariable analysis between MHDD or rrMHD and patient-specific parameters. Figure 3 shows the MHD for FB, MHDD or rrMHD against patient-specific parameters. Figure 3A-1 shows the MHD for FB versus BMI for individual patients. Figure 3A-2 and A-3 show the MHDD and rrMHD versus BMI, respectively. There was a correlation between the rrMHD and BMI (*r* = −0.248, *P* = 0.022), but there was no significant difference between the rrMHD and BMI categories (*P* = 0.147). Although the sample size of the patients with obesity was small (*n* = 4), the MHD and standard deviation were smaller than those of the other categories.

Figure 3 B-1 and B-2 show the relationship between the MHDD or rrMHD and the ratio of the lung volume. In case of all patients data, there was no correlation between the MHDD or rrMHD and ratio of lung volume. On the other hand, the correlation coefficients between the MHDD and the ratio of the lung volume for patients who received a MHD of >1.5 Gy or <1.5 Gy were 0.511 (*P* = 0.003) and 0.075 (*P* = 0.589), respectively. Similarly, the correlation coefficients between rrMHD and the ratio of the lung volume for patients who received a MHD of >1.5 Gy or <1.5 Gy were 0.602 (*P* < 0.001) and 0.092 (*P* = 0.508), respectively. A dose of 1.5 Gy was selected because it was the MHD of all patients. Figure 4 shows the correlation between the ratio of the lung volume and the BMI (*r* = 0.468, *P* < 0.001). The correlation coefficients between BMI and patient-specific parameters are tabulated in Supplementary table Table 1.

There was a correlation between the MHDD or rrMHD and chest wall displacement during DIBH. Although not shown in the figure,

the MHDD of the inner-lower (B) and outer-lower (D) quadrants tended to be higher than those of the other regions, but there were no significant differences between tumor sites (*P* = 0.854). No other patient-specific parameters were correlated with MHDD or rrMHD (Table 4).

A multivariable analysis was performed using variables that were associated with heart dose in previous studies [12, 26]. According to the multivariable analysis, the BMI and the ratio of the lung volume were significant predictors for MHDD and rrMHD (Table 5). None of the VIF values reached 1.5, which indicates that there was no collinearity in the models.

DISCUSSION

In this study, we evaluated the effect of DIBH on the dose to the heart in left-sided breast cancer patients in a large population from a single institution. Our investigation focused on Asian patients who received whole-breast irradiation after BCS to simplify the effects of patient-related parameters.

Dosimetric parameters for the heart were evaluated for the FB plans and DIBH plans, and the MHD for the FB and DIBH plans were 1.56 Gy and 0.75 Gy, respectively. These values were comparable with the MHD without DIBH in a previous study [21]. Recently, the heart doses from modern breast radiation therapy have been reported in several studies [15, 27–29]. The UK HeartSpare Study evaluated the capability and feasibility of equipment-free DIBH for 101 patients from 10 centers and reported that the dose-to-heart values for the FB and DIBH plans were 1.79 Gy and 1.04 Gy, respectively [15]. Lin *et al.* evaluated

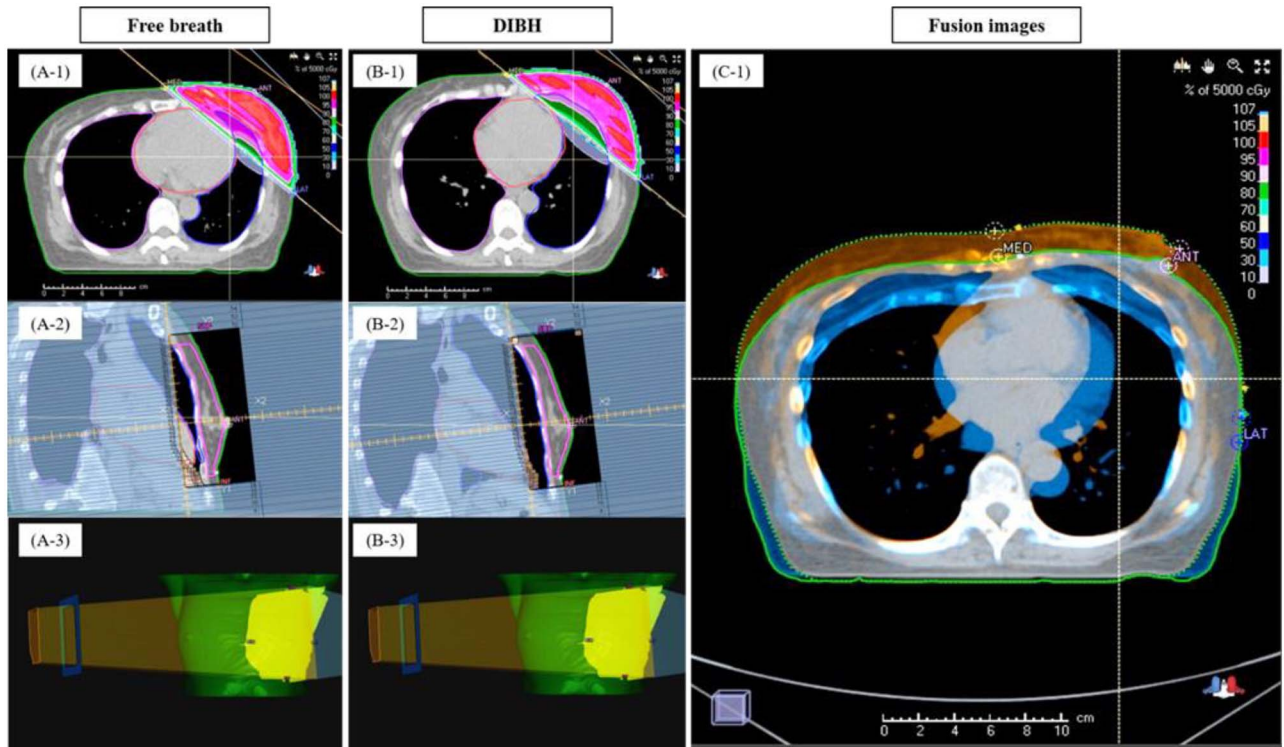


Fig. 1. Left: Example of dose distribution (A-1), beam's eye view (A-2), and radiation field on the patient's surface (A-3) for the FB plan. Middle: Example of dose distribution (B-1), beam's eye view (B-2), and radiation field on the patient's surface (B-3) for the DIBH plan. Right: Example of fusion image for FB-CT and DIBH-CT (C-1). Abbreviation: FB, free breath; DIBH, deep inspiration breath hold; CT, computed tomography.

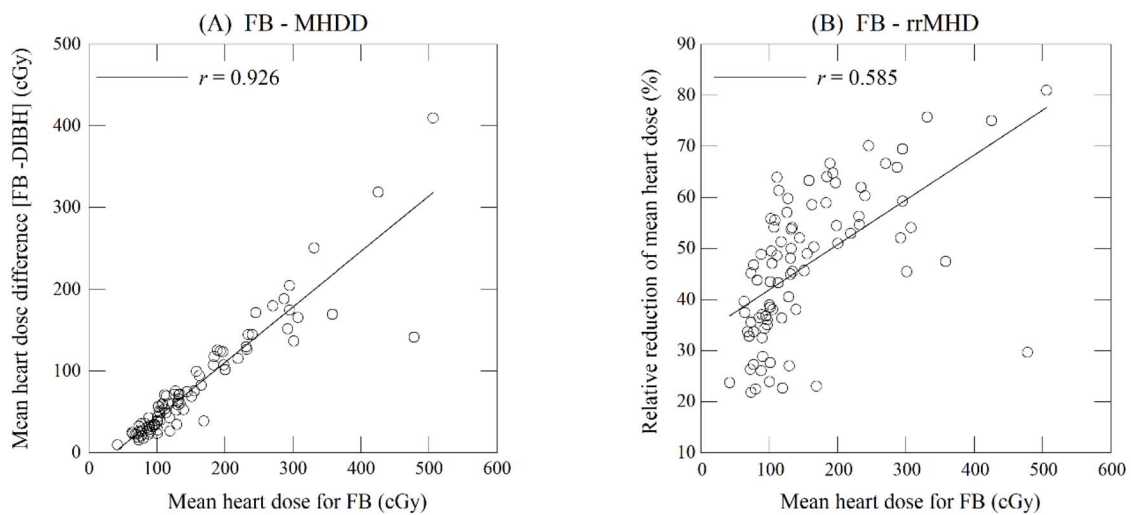


Fig. 2. (A) Mean heart dose difference and (B) relative reduction of mean heart dose by use of DIBH relative to the mean heart dose for FB plans. Abbreviation: FB, free breath; DIBH, deep inspiration breath hold; MHDD, mean heart dose difference; rrMHD, relative reduction of mean heart dose.

dose reduction of DIBH for post-mastectomy and post-BCS patients and reported that the MHD of the post-BCS patients for the FB and DIBH plans were 1.41 Gy and 0.82 Gy, respectively. Furthermore, they reported that the post-mastectomy patients obtained greater benefits

than those of the post-BCS patients because of the need to treat a much larger surgical bed [27]. Taylor *et al.* reported a MHD of 4.1 Gy for left tangential breast radiotherapy without DIBH in a systematic review of heart dose studies published from 2003 to 2013. There were no

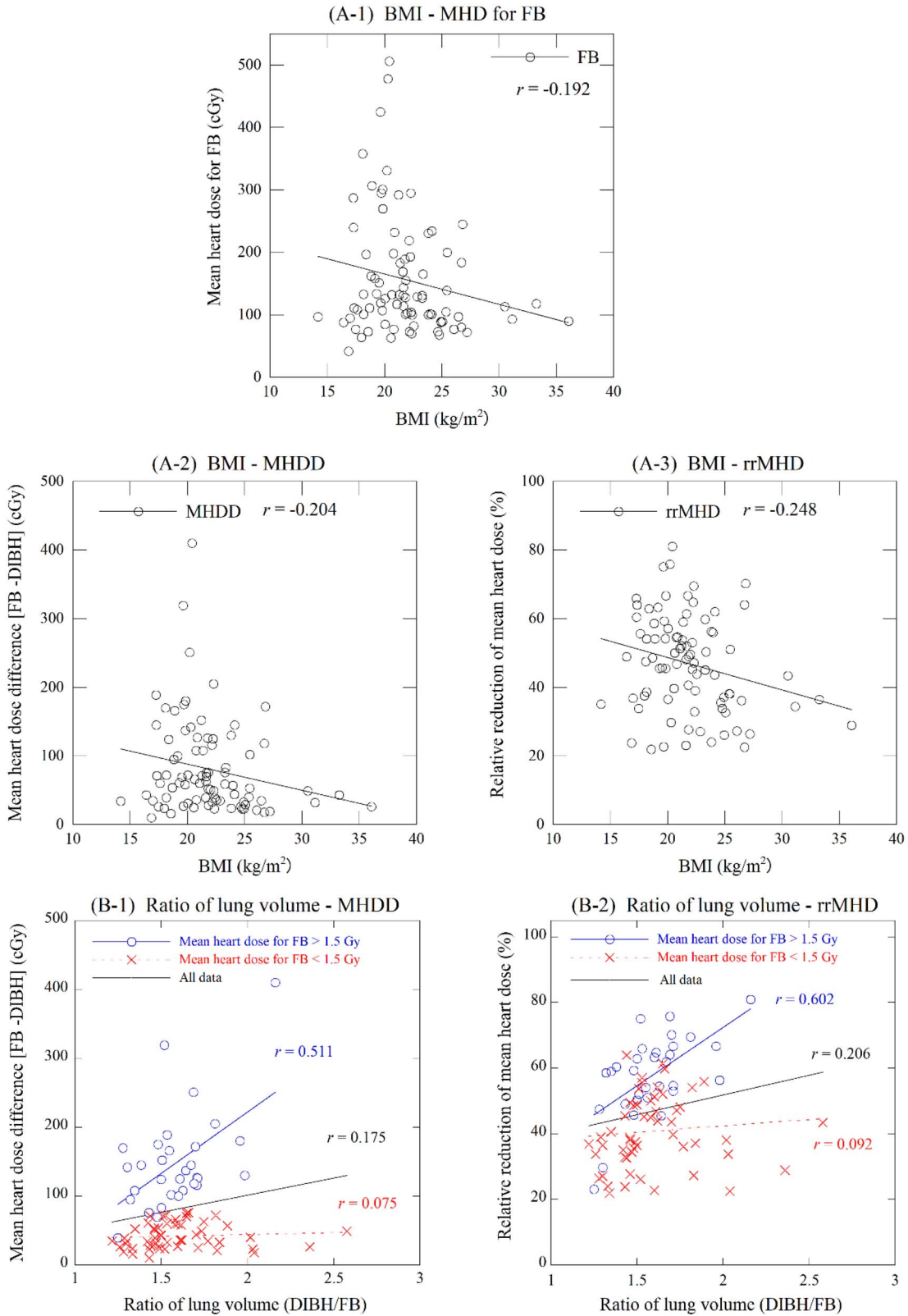


Fig. 3. Mean heart dose, absolute or relative reduction of mean heart dose against patient-specific parameters: (A-1, 2, 3) BMI, (B) ratio of lung volume between FB and DIBH. The blue circles and red crosses represent the patients who received MHD of >1.5 Gy and <1.5 Gy, respectively. Abbreviations: BMI, body mass index; FB, free breath; DIBH, deep inspiration breath hold.

Table 5. Multivariable analysis of predictors of absolute and relative reduction of mean heart dose

Variables	β (95% CI)	P-value
MHDD		
BMI	-5.51 (-9.94 - 1.08)	0.015
Ratio of lung volume	83.30 (16.56-150.04)	0.015
Chest-wall displacement	39.30 (-1.69-80.28)	0.06
rrMHD		
BMI	-0.014 (-0.023 - 0.006)	0.002
Ratio of lung volume	0.211 (0.080-0.344)	0.002
Chest-wall displacement	0.073 (-0.008-0.155)	0.076

MHDD = mean heart dose difference, rrMHD = relative reduction of mean heart dose, BMI = body mass index, β = regression coefficient, CI = confidence interval.

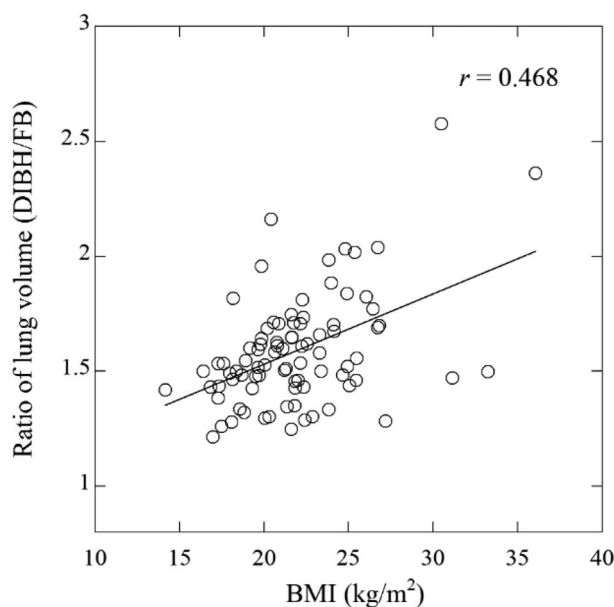


Fig. 4. Ratio of lung volume between FB and DIBH against BMI. Abbreviations: BMI, body mass index; FB, free breath; DIBH, deep inspiration breath hold.

significant differences in heart doses between world regions (Europe reported 3.9 Gy in 43 studies, North America reported 3.5 Gy in 22 studies, and Asia reported 4.7 Gy in 35 studies). However, there were significant deviations in heart doses between countries within Europe (the highest values reported in Europe for Germany (6.5 Gy) and the lowest values reported in Europe for the UK (1.6 Gy)) and Asia (the highest values reported in Asia for Saudi Arabia (7.9 Gy) and the lowest values reported in Asia for Japan (3.4 Gy)). A MHD value of 1.3 Gy for left tangential breast radiotherapy with breathing control has been reported in 14 studies [28]. These large variabilities in reported heart doses between countries and reports may reflect differences in patient anatomy, radiotherapy technique, targets, and delineation of the heart.

Focusing on patient-specific parameters, the MHDD and rrMHD were correlated with inspiration-related factors such as chest wall displacement and the ratio of the lung volume for patients who received a high MHD (Fig. 3B-1 and B-2). These are significant predictors of benefit of DIBH in the reduction of heart doses. The mean rrMHD

was 46.9% (range, 21.9%–81.0%), and there was a large deviation between patients (Fig. 2). A MHD of ~0.6 Gy has been reported, even if the heart was not in the radiation field for right- or left-sided breast radiotherapy [29], so the relative reduction for patients who received a low dose to the heart in FB was low. Of the 85 patients, only 1 patient deviated greatly from the tendency to a relationship between MHD for FB and rrMHD (Patient 6, MHD for FB: 4.78 Gy, rrMHD: 29.7%). An interesting finding was that this patient could not perform deep breathing, so the lung volume difference between FB and DIBH was the smallest of all patients (lung volume difference: 568.8 cm³, ratio of lung volume: 1.30). Therefore, patients with high heart doses may need to have sufficient inspiratory volume to benefit from DIBH. Although inspiratory volume changes because of differences in BMI, an absolute inspiratory volume of ≥ 1000 cm³ and ratio of lung volume of ≥ 1.4 appeared to be the threshold volume as a result of additional analysis of patients with relative dose reduction of 50% or more (see Supplementary figure 1). Wang *et al.* also reported similar results with respect to heart $V_{50\%}$ and their threshold volume was 800 cm³ [12]. It might be necessary to achieve a minimum inspiratory volume even in patients with a small physique and a small inspiratory volume. These values require verification in a larger cohort of patients.

In our cohort, the mean BMI was 21.9 kg/m², and there were only a few patients who were categorized as overweight or obese, which means that the cohort included many underweight patients; however, the distribution of this population was similar to those in previous reports [16, 17]. The reduction in heart dose could be affected by differences in body shape and anatomical changes, and there was significant difference in the magnitude of dose reduction due to differences in BMI. There is a negative correlation between heart dose for FB and BMI, and patients with a lower BMI tend to have higher heart doses and greater dose reductions. The tangential beams are typically arranged for treating just the target (breast), and the field edges pass through the heart and lung. As shown in Supplementary figure 2, the beam path may change as it passes through the lungs and heart because of the BMI. For patients with a high BMI, the beams are arranged in a way to make it difficult for it to pass through the heart and lung because of fat. On the other hand, it is the opposite for those patients who are underweight. Consequently, there was negative correlation between BMI and Lung- $V_{20\text{Gy}}$, and the heart and lung were mostly not included in the radiation field for patients with high BMI (Supplementary figure 3). However, there are several reports of a correlation between heart dose and BMI, and opinions are divergent [26, 30]. Mkanna *et al.* reported

that larger BMI was associated with increased MHD [26]. Our study focused on BCS patients only, whereas their cohort mainly included patients who had undergone mastectomy (97%). An interesting finding in our cohort was that patients with a higher BMI tended to have a lower MHD for FB, even though volume of heart correlated with BMI (Supplementary table Table 1). Generally, it would be expected that the heart dose will be higher if the heart is large. However, this hypothesis may not be applicable to whole-breast irradiation in patients with a high BMI, because of the presence of fat or soft-tissue. Therefore post-mastectomy patients may have different results even if they do have a high BMI, because they do not have presternal fat and require radiation of a larger surgical bed. Because the relationship between heart dose and BMI is affected by various factors such as individual patient-specific parameters (thorax shape, breast size and shape, etc.) and beam arrangement, further verification in a large population including patients with high BMI is required.

A limitation of this study is that the dose to sub-cardiac structures, such as the left anterior descending (LAD) artery, were not evaluated. Delineation of the LAD artery has a large inter-observer error and requires robust contouring, so this investigation excluded dosimetric analysis of the LAD artery. However, there is a correlation between heart and LAD artery doses, and it is possible to estimate the effects of heart doses on the LAD artery [12].

Implementation of DIBH needs additional resources, such as a respiratory motion tracking system, and extra time, cost, and burden on clinical staff. It may not be feasible to apply DIBH for all left-sided breast cancer patients. Quantitative evaluation of the mean dose and relative reduction in heart dose and patient-specific parameters such as BMI can aid patient selection for DIBH. We recommend that implementation of DIBH is considered as a possibility for underweight- and normal-BMI patients. We plan to further investigate this topic by considering the selection of patient-specific parameters and the use of images.

In conclusion, we evaluated the reduction of radiotherapeutic dose to the heart by the use of DIBH and found that DIBH gave an ~50% reduction in dose relative to that from use of a FB plan. The degree of benefit from DIBH varied with each patient, and the patients with low BMI benefited more from DIBH.

SUPPLEMENTARY DATA

Supplementary data are available at the *Journal of Radiation Research* online.

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CONFLICT OF INTEREST

The authors state that they have no relevant conflicts of interest to disclose.

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