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Original Article

Investigation into the Effect of Breast Volume on Irradiation Dose Distribution in Asian Women with Breast Cancer

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Reports on irradiation dose distribution in breast cancer radiotherapy with sufficient sample size are limited in Asian patients. Elucidating dose distribution in Asian patients is particularly important as their breast volume differs compared to patients in Europe and North America. Here, we examined dose distribution in the irradiation field relative to breast volume for three irradiation methods historically used in our facility. We investigated the influence of breast volume on each irradiation method for Asian women. A total of 573 women with early-stage breast cancer were treated with breast-conserving surgery and adjuvant radiotherapy. Three methods were compared: wedge (W), field-in-field (FIF), and wedge-field-in-field (W-FIF). In patients with small breast volume, FIF decreased low- and high-dose areas within the planning target volume, and increased optimal dose area more than W. In patients with medium and large breast volumes, FIF decreased high-dose area more than W. The absolute values of correlation coefficients of breast volume to low-, optimal-, and high-dose areas and mean dose were significantly lower in FIF than in W. The correlation coefficients of V107% were 0.00 and 0.28 for FIF and W, respectively. FIF is an excellent irradiation method that is less affected by breast volume than W in Asian breast cancer patients.

Key words: breast cancer, radiotherapy, dose distribution, irradiation method, breast volume

Radiotherapy for breast cancer reduces local recurrence and improves survival [1,2]. To date, various irradiation techniques have been applied clinically [3-19], and advances in irradiation techniques have reduced adverse events for organs at risk (OAR) [5,16]. Different irradiation techniques can be used to modify the dose distributions to the skin, lungs, and heart, which also affects the rate of adverse events at these sites. Skin damage is known to be associated with high doses in the irradiation field [10,12,13]. The mean heart dose (MHD) correlates with the risk of adverse

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events for both the heart and coronary arteries [13-17]. In addition, the risk of radiation pneumonitis is proportional to the mean lung dose [13,14].

Breast cancer patients with large breast volume have been reported to experience uneven dose distributions [8,10] and higher rates of adverse events [5,9,10,13] than those with smaller breast volume. Nonetheless, few large studies have compiled the irradiation dose distributions for Asian women with breast cancer, whose breast volumes tend to be smaller than those of Western women [18].

In this study, we reviewed the breast volumes and irradiation dose distributions for Asian women with breast cancer who were treated at our institution using one of three different irradiation methods: the wedge method (W), field-in-field method (FIF), or wedge-field-in-field method (W-FIF), which combines the W and FIF methods. We then analyzed the relation between the differences in breast volume and the dose distribution for each irradiation method, and compared the results with data acquired from a literature review. In this way, we attempted to determine which irradiation method is least affected by differences in breast volume. In addition, we aimed to grasp the actual irradiation doses for targets and OARs of a large number of Asian breast cancer patients, compare them with past literature data, and use the results for future improvement.

Patients and methods

Patients. This study evaluated 577 women with breast cancer without distant metastasis, who were treated with breast-conserving surgery and adjuvant radiation therapy at Okayama University Hospital between April 2008 and December 2016. The exclusion criteria were simultaneous treatment of bilateral breast cancer, irradiation treatment of the regional lymph nodes, or hypofractionated irradiation. The Ethical Review Board of our institute approved the use of anonymous post-radiation therapy data for the study (No. KEN 1907-027). The study was conducted in accordance with the 2013 revised Helsinki Declaration.

Radiation treatment. Each patient received whole breast radiation therapy at a total prescribed dose of 50 Gy in 25 fractions (2 Gy per fraction, 5 times a week). Some patients received a 10 or 16 Gy boost irradiation to the tumor bed. Computed tomography (CT) imaging was performed with patients in a supine position, with one or both arms extended overhead, and a foam cushion wedge under the knee, with or without fasteners. CT with free-breathing was performed using an Asteion Super 4 Edition multi-slice CT scanner (Toshiba Medical Systems, Tochigi, Japan), and reconstruction was performed on 2-mm thick slices. In order to facilitate contour setting in the CT image during the setting of the irradiation field, radiopaque markers were placed on the following body surface landmarks: the suprasternal notch, sternal midline, midaxillary line, 1 cm inferior to the inframammary fold, surgical scars, nipples, and the edges of palpable breast tissue. The CT images were then transferred to a treatment planning system, CMS XiO Ver 4.3.4 (Computerized Medical Systems, Maryland Heights, MO, USA).

The irradiation field was preset following the suprasternal notch, the sternal midline, the midaxillary line, and 1 cm inferior of the inframammary fold, and extended 2 cm on the skin side. The preset irradiation field was verified and modified to include the planning target volume (PTV) and breast PTV evaluation (BPe) in an irradiation field that would result in three-dimensional conformal radiotherapy treatment. The PTV was pre-set three-dimensionally as a 5 mm area inside the irradiation field and excluded the following: the patient's extracorporeal air, tissue 5 mm below the skin, the lung and the chest wall between the lung and the anterior rib edge. The BPe was determined according to the clinical target volume and PTV which were defined by the clinical research protocol RTOG 1005 <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=open File&FileID=9366 (accessed July 11, 2020)>.

The axillary lymph node levels I, II, and III, and OAR were contoured following the RTOG-approved consensus guidelines for delineating breast cancer targets and normal structures <https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx (accessed July 11, 2020)>. The outlined OAR were the lungs and the heart. The lungs were outlined by automatic segmentation with manual verification. The contour of the heart began slightly below the level at which the pulmonary trunk diverged into the left and right pulmonary arteries, and was contoured to the lowest extent near the diaphragm in all subsequent slices. Treatment was planned in an isocentric manner using the CMS XiO treatment planning system. Beam energies of 4, 6, and 10 MV were used as high energy X-rays from a Linac (Mevatron M2/6327, Primus High Energy KD2/7467, and ONCOR High Energy ONCR-K; Toshiba Medical Systems, Tochigi, Japan).

Three irradiation methods were performed. The W was used as follows: 2 tangential opposing wedge half beams were generated to cover the field. Gantry and collimator angles were adjusted using the beam's eye view of the treatment planning system to minimize heart and lung irradiation while maximizing the target volume range. The reference point (RP) was set at the level of the nipple, or at an intermediate level between the upper and lower ends of the irradiation field. A physical wedge filter was used on the opposing tangential beams to improve the target dose distribution. The W-FIF was used as follows. When the wedge filter alone could not improve the dose distribution, it was improved by adding an additional tangential field-in-field to avoid hot spots. The RP was set at the level of the nipple, or at an intermediate level between the upper and lower ends of the irradiation field. FIF was used as follows. Two opposing tangential fields were set without a wedge filter. The RPs were set at the point on a slice at an intermediate level between the upper and lower borders of the field, the deepest point on a slice 2 cm inside from the upper border of the field, or both simultaneously. The main field was copied as a subfield, and a multileaf collimator was set up to protect the areas of the breast that received high doses. The PTV and BPe doses were set according to the ICRU criteria such that the dose distribution was 95-107% of the prescribed dose, and the OAR dose was as low as possible. The irradiation methods W, W-FIF, and FIF were used for patients in this order sequentially over the research period.

The dosimetric parameters of the targets evaluated in this study were as follows: mean dose of PTV and BPe, V0-95% (volume fraction receiving less than 95% of the prescribed dose); V95-107% (volume fraction of 95-107% of the prescribed dose); V107% (volume fraction receiving more than 107% of the prescribed dose); V105% (volume fraction of 105% or more of the prescribed dose); and the mean dose to axillary lymph node levels I, II, and III. The dosimetric parameters of the OAR were as follows: ipsilateral pulmonary (ip) mean dose, ipV20 (volume fraction receiving ≥ 20 Gy), and ipV30 (volume fraction receiving ≥ 30 Gy); MHD, V10 (volume fraction receiving ≥ 10 Gy), and V20 (volume fraction receiving ≥ 20 Gy) of the heart; and the maximum doses for the left anterior descending coronary artery (LAD), left circumflex coronary artery (CCA), and right coronary artery (RCA).

Data collection and statistical analysis. For each patient, we analyzed the patient background factors and the dosimetric parameters obtained from the dose-volume histogram in the radiation treatment plan. BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo) was used for statistical analysis. Differences in patient background factors and dosimetry parameters were compared using the chi-square test or Kruskal-Wallis test followed by the Scheffe method, depending on the irradiation method used. Differences in dosimetry parameters, *etc.*, by irradiation methods and breast volume were also compared using the Kruskal-Wallis test and the Scheffe method.

In order to evaluate the relationship between breast volume and dose parameter for each irradiation method, Spearman's rank correlation coefficient (r_s) was calculated, and the significance was tested. The absolute value of r_s was defined as "very weak" 0-0.19; "weak" 0.20-0.39; "moderate" 0.40-0.59; "strong" 0.60-0.79; and "very strong" 0.80-1. Fisher Z-transform with a two-sided test was performed to test for significant differences in r_s for each treatment method. A *P*-value < 0.05 was considered statistically significant. Calculation of the 95% confidence interval (CI) for r_s was performed using langtest < http://langtest.jp/shiny/cor/ (accessed September 30, 2020)>.

Results

Between 2008 and 2016, 577 patients between the ages of 24 and 82 (median, 55) were treated according to the inclusion criteria. Four patients treated without using a W or FIF technique were excluded from this study due to insufficient sample size; thus, a total of 573 patients were included in the final analysis. The W, W-FIF, and FIF were used on 109, 69, and 395 patients, respectively.

Table 1 presents the background factors for each irradiation method. The mean age of the patients was 55 ± 11 years. There were no statistically significant differences in age or tumor site, as defined by the international classification of diseases for oncology <https://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf?sequence=1 (accessed September

26, 2020)>, among the three irradiation groups. BPe volume was used to evaluate the breast volume, and the breast volume for the W-FIF group was larger than that for the W group. Regarding the background factors of patients with left breast cancer, there were no significant differences in age, tumor site or breast volume among the three irradiation groups (Table 1).

Breast volume was divided into 3 groups (small: <360; medium: ≥ 360 and ≤ 568; large: >568 [cm^3]) according to the same criteria in previous reports [6]. The dose parameters for each group are summarized in Table 2. With regards to the target, in patients with a small breast volume, FIF decreased low and high dose areas within the PTV and increased the optimal dose area more than W. In patients with medium and large breast volumes, FIF decreased the high dose area more than W. As breast volume increased, both FIF and W decreased the low dose area.

The correlation coefficients (r_s) and 95% CIs between the breast volume and each dose parameter are listed in Table 3 for each irradiation method. With regards to the evaluation of r_s for the targets, the mean dose with W and W-FIF and the low-dose area (V0-95%) with W-FIF were "weak"; the low-dose area (V0-95%) with W was "moderate"; and all parameters with FIF were "very weak". As a result of the Z conversion, the absolute values of r_s were significantly lower with FIF than with W in the low-, optimal-, and high-dose areas and mean dose (Table 3).

With respect to irradiation to the lymph nodes, W and W-FIF are the methods in which breast volume has a significant effect on dose distribution, while distribution to the lymph nodes by FIF is not affected by breast volume (Table 3).

With respect to OAR (Table 2), the ip mean lung dose decreased with increasing breast volume by all three irradiation methods. The r_s for all lung dose parameters (ip mean dose, ipV20, and ipV30) were "weak" for W and FIF, and "moderate" for W-FIF. No significant differences were found in these r_s values by Z-transform (Table 3). The MHD of FIF was smaller than that of W for patients with small breast volumes (Table 2). The MHD increased in FIF as breast volume increased (Table 2). The r_s for the MHD (Table 3) was "moderate" for FIF, "weak" for W-FIF, and "very weak" for W. The r_s values for V10 and V20 (Table 3) were

Table 1 Background factors for each irradiation method

	All methods	W	W-FIF	FIF	Statistics (W vs W-FIF vs FIF)
All patients					
Patient	573	109	69	395	
Age	55 ± 11	54 ± 10	53 ± 12	55 ± 11	NS*
Tumor site in breast#					NS**
Upper-inner quadrant	161	29	18	114	
Lower-inner quadrant	50	14	4	32	
Upper-outer quadrant	278	44	37	197	
Lower-outer quadrant	55	18	5	32	
Central portion	29	4	5	20	
Breast volume (cm^3)	442 ± 254	410 ± 234	532 ± 308	435 ± 246	$P<0.05$* ($P<0.05$‡)
Patients of left breast cancer					
Patient	296	49	40	207	
Age	55 ± 11	55 ± 10	55 ± 13	55 ± 11	NS*
Tumor site in breast#					NS**
Upper-inner quadrant	82	17	9	56	
Lower-inner quadrant	30	8	3	19	
Upper-outer quadrant	149	18	24	107	
Lower-outer quadrant	16	4	2	10	
Central portion	19	2	2	15	
Breast volume (cm^3)	442 ± 253	452 ± 249	494 ± 262	430 ± 252	NS*

Number with "±" indicates mean with standard deviation. Numbers in "patient" and "tumor site in breast" indicate numbers of patients.
#, International classification of diseases for oncology (third edition).
*, Kruskal-Wallis test; **, Chi-square test; ‡, W vsW-FIF for Scheffe's method of Kruskal-Wallis test.
W, wedge method; W-FIF, wedge field-in-field method; FIF, field-in-field method; NS, not significant.

Table 2 Dose parameters relative to breast volume for each irradiation method

Breast size classification		Irradiation method	Patient number (Left)	Breast volume (cm^3)	PTV: Dose parameter: Mean dose (cGy)	PTV: Dose parameter: V0–95%	PTV: Dose parameter: V95–107%	PTV: Dose parameter: V107%	PTV: Dose parameter: V105%	OAR: Lung: ip mean dose (cGy)	OAR: Heart*: Mean dose (cGy)
Breast volume (cm^3)	Small (<360)	All	258 (126)	244 ± 78	4,943 ± 76	15.0 ± 8.0	84.8 ± 7.9	0.22 ± 0.92	2.40 ± 3.90	755 ± 180	249 ± 99
		W	59 (19)	257 ± 71	4,896 ± 94	18.2 ± 8.5	81.1 ± 7.9	0.68 ± 1.84	3.51 ± 5.44	712 ± 151	318 ± 116
		W-FIF	23 (14)	258 ± 62	4,896 ± 69	18.6 ± 7.2	81.4 ± 7.2	0.01 ± 0.01 §	2.04 ± 1.65	718 ± 125	289 ± 96
		FIF	176 (93)	237 ± 81	4,965 ± 59 †††,‡‡‡	13.5 ± 7.5 †††,‡‡	86.4 ± 7.5 †††,‡‡	0.10 ± 0.19	2.08 ± 3.41 †††,‡	774 ± 192 †	230 ± 88 ††,‡
	Medium (≥360.0–≤568.0)	All	178 (97)	455 ± 57	4,976 ± 63	10.1 ± 6.0	89.8 ± 5.8	0.19 ± 0.58	2.92 ± 4.37	705 ± 199	271 ± 75
		W	28 (17)	459 ± 64	4,949 ± 78	11.4 ± 7.7	87.9 ± 7.0	0.72 ± 1.23	4.35 ± 5.15	668 ± 169	294 ± 88
		W-FIF	24 (15)	459 ± 48	4,940 ± 69	13.4 ± 6.2	86.6 ± 6.2	0.00 ± 0.00 §§§	2.34 ± 2.10	580 ± 110	300 ± 58
		FIF	126 (65)	454 ± 58	4,989 ± 53 †,‡‡	9.1 ± 5.2 ‡‡	90.8 ± 5.2 ‡‡	0.10 ± 0.26 †††,‡	2.71 ± 4.46 †††,‡	737 ± 208 ‡‡‡	259 ± 73 ‡
	Large (>568)	All	137 (73)	798 ± 229	4,962 ± 69	12.3 ± 7.1	87.4 ± 6.9	0.30 ± 1.08	3.27 ± 4.88	622 ± 210	287 ± 85
		W	22 (13)	755 ± 264	4,961 ± 92	10.8 ± 7.0	87.7 ± 6.0	1.50 ± 2.37	6.19 ± 7.77	624 ± 268	298 ± 153
		W-FIF	22 (11)	898 ± 267 §§	4,943 ± 54	13.3 ± 5.6	86.7 ± 5.6	0.00 ± 0.01 §§§	2.51 ± 1.82	567 ± 186	296 ± 58
		FIF	93 (49)	784 ± 205	4,966 ± 66	12.4 ± 7.5	87.5 ± 7.5	0.09 ± 0.19 †††,‡	2.77 ± 4.26 †††,‡	634 ± 200	282 ± 64
Statistics		W		$P<0.001$	$P<0.01$	$P<0.001$	$P<0.001$	NS	NS	$P<0.05$	NS
		W-FIF		$P<0.001$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$	NS	$P<0.001$	NS
		FIF		$P<0.001$	$P<0.01$	$P<0.001$	$P<0.001$	NS	NS	$P<0.001$	$P<0.001$

Number with "±" indicates mean with standard deviation, respectively. "Patient number (Left)" indicates number of all patients and number of patients of left breast cancer in parentheses.
*, analysis for patients of left breast cancer. PTV, planning target volume; OAR, organ at risk; ip, ipsilateral pulmonary; W, wedge method; W-FIF, wedge field-in-field method; FIF, field-in-field method; NS, not significant.
§, W vs W-FIF; †, W vs FIF; ‡, W-FIF vs FIF for Scheffe's method of Kruskal-Wallis test for comparison of irradiation methods in each group of breast volume, respectively. §,† and ‡, $P<0.05$; §§,†† and ‡‡, $P<0.01$; §§§,††† and ‡‡‡, $P<0.001$, respectively. $P<0.05$, $P<0.01$, $P<0.001$ and NS for Kruskal-Wallis test in each irradiation method for comparison among small, medium and large groups of breast volume.

"very weak" and "very weak" in W, "very weak" and "weak" in W-FIF, and "weak" and "weak" in FIF, respectively. In the Z-transform, the r_s for the MHD was significantly different between FIF and W.

With regard to the coronary arteries, the LAD had a higher dose than the CCA and RCA (Table 4). The r_s of LAD with respect to breast volume was "very weak" for W and FIF, and "weak" for W-FIF (Table 3). No significant difference was found in these r_s values by Z-transform (Table 3).

Table 4 summarizes the dose parameters for each irradiation method. Regarding the target, the high-dose area in PTV and BPe was greater with W than with FIF. The low-dose area in PTV and BPe was greater with W than with FIF. In the OAR, FIF decreased the MHD and maximum doses of the CCA and RCA significantly more than W and W-FIF.

Discussion

Few reports have examined the differences in irradiation techniques in a large number of breast cancer patients in Asia, where breast volume is relatively small compared to Europe and North America. In this study, the characteristics of each irradiation method were analyzed statistically in a large number of cases in order to improve the reliability of the data. As a result, it was clarified that FIF is an excellent irradiation method with a smaller high-dose area than that by W irrespective of breast volume.

In the studies from Asia (including Japan) [18] that have examined the differences in irradiation techniques, the number of cases has been small (10 to <100). There are few reports of more than several hundred cases even in Europe and North America [4,6-10,12]. This study used a large number of cases, 573, to compare treatments with previous reports [6] in Europe and North America.

The mean breast volume in European and North American patients is 518-1,063 (cm^3) [6,12,19]; in contrast, in this study of Asian patients, the mean breast volume was 442 (cm^3). Numerous studies have shown that large breast volume affects the high-dose area of the target

Table 3 Correlation coefficients between breast volumes and dose parameters for each irradiation method

Dose parameters		W		W-FIF		FIF		Statistics
		r_s	95% CI (lower, upper)	r_s	95% CI (lower, upper)	r_s	95% CI (lower, upper)	
All patients								
Target								
PTV	Mean dose (cGy)	0.37***	(0.197, 0.523)	0.30*	(0.069, 0.502)	0.08	(−0.014, 0.182)	*P*<0.01‡‡
	V0−95%	−0.45***	(−0.586, −0.282)	−0.33**	(−0.528, −0.104)	−0.18***	(−0.273, −0.082)	*P*<0.01‡‡
	V95−107%	0.44***	(0.281, 0.584)	0.33**	(0.104, 0.528)	0.18***	(0.083, 0.274)	*P*<0.01‡‡
	V107%	0.28**	(0.099, 0.446)	−0.26*	(−0.464, −0.020)	0.00	(−0.102, 0.096)	*P*<0.001‡, *P*<0.01‡‡, *P*<0.05‡‡‡
	V105%	0.20*	(0.015, 0.376)	0.12	(−0.117, 0.350)	0.05	(−0.053, 0.144)	NS
ALN	Level I mean dose (cGy)	0.38***	(0.205, 0.529)	0.40***	(0.178, 0.580)	0.16**	(0.060, 0.252)	*P*<0.05‡‡, ‡‡‡
	Level II mean dose (cGy)	0.32***	(0.143, 0.481)	0.38**	(0.152, 0.562)	0.19***	(0.096, 0.286)	NS
	Level III mean dose (cGy)	0.32***	(0.139, 0.478)	0.36**	(0.140, 0.553)	0.14**	(0.047, 0.240)	NS
OAR								
Lung	ip mean dose (cGy)	−0.32***	(−0.476, −0.137)	−0.44***	(−0.609, −0.220)	−0.29***	(−0.378, −0.197)	NS
	ipV20 (%)	−0.36***	(−0.518, −0.190)	−0.47***	(−0.635, −0.261)	−0.32***	(−0.403, −0.225)	NS
	ipV30 (%)	−0.34***	(−0.495, −0.160)	−0.46***	(−0.625, −0.246)	−0.31***	(−0.401, −0.223)	NS
Patients of left breast cancer								
OAR								
Heart	Mean dose (cGy)	0.02	(−0.264, 0.298)	0.21	(−0.104, 0.493)	0.41***	(0.288, 0.516)	*P*<0.05‡‡
	V10 (%)	−0.03	(−0.310, 0.252)	0.19	(−0.124, 0.478)	0.26***	(0.125, 0.380)	NS
	V20 (%)	0.03	(−0.261, 0.301)	0.28	(−0.044, 0.537)	0.27***	(0.135, 0.388)	NS
	LAD maximum dose (cGy)	−0.02	(−0.303, 0.259)	0.26	(−0.052, 0.531)	0.03	(−0.104, 0.169)	NS
	CCA maximum dose (cGy)	0.13	(−0.156, 0.397)	0.05	(−0.267, 0.355)	0.53***	(0.427, 0.624)	*P*<0.01‡‡, ‡‡‡
	RCA maximum dose (cGy)	−0.06	(−0.338, 0.222)	−0.21	(−0.486, 0.114)	0.37***	(0.248, 0.483)	*P*<0.01‡‡, *P*<0.001‡‡‡

*, *P*<0.05; **, *P*<0.01; ***, *P*<0.001 for Spearman's rank correlation coefficient, respectively.
‡, W vs W-FIF; ‡‡, W vs FIF; ‡‡‡, W-FIF vs FIF; NS, not significant for Fisher's Z-transform for significant differences in r_s, respectively. W, wedge method; W-FIF, wedge field-in-field method; FIF, field-in-field method; r_s, Spearman's rank correlation coefficient; CI, confidence interval; PTV, planning target volume; ALN, axillary lymph node; OAR, organ at risk; ip, ipsilateral pulmonary; LAD, left anterior descending coronary artery; CCA, left circumflex coronary artery; RCA, right coronary artery.

[8,10] and increases adverse skin effects [5,9,10,13]. Morganti *et al.* [6], using the same 3 volumetric categories as in this study, found that FIF decreased the high dose area more than W at any breast volume. Similarly, in this study, where we used the correlation coefficient for the target, we found that the absolute values of r_s were significantly lower in FIF than in W in the mean-dose, low-dose, optimal-dose, and high-dose areas. It can be expected that using FIF to reduce the high-dose area could also decrease adverse skin events. In patients with small breast volume, FIF decreased not only the high-dose area but also the low-dose area, and increased the optimal-dose area more than W, suggesting that FIF is a superior method. The high-dose areas of all irradiation methods in this study were less irrespective of breast volume than those in Morganti *et al.* and other reports [6,9] from Europe and North America.

With regard to OAR, as breast volume increased, the mean lung dose decreased with all irradiation methods, and MHD increased with FIF. Compared to previous papers [4,6], the mean lung dose in this study was higher. Moreover, Osei *et al.* reported lower ipV20 and ipV30 using state-of-the-art deep inspiration breath hold (DIBH) technology [8] compared to our results. The MHDs in this study were higher, but the V10 and V20 were lower than those in previous papers using IMRT and FIF [4,6,19]. Osei *et al.* also reported a lower V10 and V20 using the state-of-the-art DIBH technology [8] compared to our results. In our study, the MHD of FIF was lower than those of W and W-FIF.

When using FIF, the MHD is greatly affected by breast volume; thus, it is desirable to use DIBH in patients with large breasts. Oechsner *et al.* [3] reported that DIBH reduced MHD by 31-63% compared to free breathing. Beaton *et al.* [16] reported that radiation-induced cardiac death by 10 years is low if the MHD is less than 3.3 Gy. In this study, 18% (52/296) of the total, 29% (14/49) of W, 23% (9/40) of W-FIF, and 14% (29/207) of FIF cases had an MHD greater than 3.3 Gy. If the maximum LAD dose is less than 45.4 Gy, cardiac death from radiation by 10 years is low [16]. In this study, 18% (54/296) of the total, 37% (18/49) of W, 15% (6/40) of W-FIF, and 14% (30/207) of FIF cases had maximum LAD doses greater than 45.4 Gy. From this, FIF can be expected to reduce adverse heart events to a greater extent than conventional W.

As of 2016 in Japan [20], FIF had become a main-

Table 4 Summary of dose parameters for each irradiation method

Irradiation method			W	W-FIF	FIF	Statistics (W vs W-FIF vs FIF)
All patients						
Patient			109	69	395	
Target						
	PTV	Volume (cm^3)	554 ± 303	652 ± 348	572 ± 303	NS*
		Mean dose (cGy)	$4{,}923 \pm 94$	$4{,}926 \pm 67$	$4{,}973 \pm 60$	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V0–95%	15 ± 9	15 ± 7	12 ± 7	$P<0.001$* ($P<0.01^{\ddagger\ddagger}$, $P<0.001^{\ddagger\ddagger\ddagger}$)
		V95–107%	84 ± 8	85 ± 7	88 ± 7	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V107%	0.86 ± 1.84	0.00 ± 0.01	0.10 ± 0.21	$P<0.001$* ($P<0.001^{\ddagger, \ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V105%	4.27 ± 5.94	2.29 ± 1.85	2.44 ± 3.98	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
	BPe	Mean dose (cGy)	$4{,}968 \pm 68$	$4{,}970 \pm 53$	$5{,}002 \pm 61$	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V0–95%	9 ± 6	11 ± 7	7 ± 6	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V95–107%	90 ± 5	89 ± 7	93 ± 6	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V107%	0.68 ± 1.81	0.00 ± 0.01	0.09 ± 0.24	$P<0.001$* ($P<0.01^{\ddagger\ddagger\ddagger}$, $P<0.001^{\ddagger, \ddagger\ddagger}$)
		V105%	3.84 ± 5.93	2.31 ± 2.06	2.55 ± 4.32	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
	ALN	Mean dose (cGy)				
		Level I	$2{,}966 \pm 731$	$2{,}869 \pm 695$	$3{,}368 \pm 805$	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		Level II	$1{,}365 \pm 998$	$1{,}341 \pm 1{,}084$	$1{,}552 \pm 1{,}209$	NS*
		Level III	359 ± 406	355 ± 390	456 ± 543	NS*
OAR						
	Lung	ip mean dose (cGy)	683 ± 186	621 ± 156	729 ± 206	$P<0.001$* ($P<0.001^{\ddagger\ddagger\ddagger}$)
		ipV20 (%)	12 ± 4	10 ± 4	13 ± 5	$P<0.001$* ($P<0.05^{\ddagger\ddagger}$, $P<0.001^{\ddagger\ddagger\ddagger}$)
		ipV30 (%)	9 ± 4	8 ± 3	10 ± 4	$P<0.001$* ($P<0.01^{\ddagger\ddagger}$, $P<0.001^{\ddagger\ddagger\ddagger}$)
Patients of left breast cancer						
Patient			49	40	207	
Target						
	PTV	Volume (cm^3)	608 ± 323	613 ± 324	566 ± 308	NS*
OAR						
	Heart	Mean dose (cGy)	304 ± 117	295 ± 72	251 ± 81	$P<0.001$* ($P<0.01^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		V10 (%)	4.0 ± 3.4	3.7 ± 2.2	3.0 ± 2.3	$P<0.05$*
		V20 (%)	2.2 ± 2.5	1.8 ± 1.5	1.5 ± 1.6	NS*
		LAD maximum dose (cGy)	$3{,}478 \pm 1{,}351$	$3{,}629 \pm 1{,}069$	$3{,}058 \pm 1{,}388$	$P<0.05$*
		CCA maximum dose (cGy)	240 ± 34	238 ± 31	205 ± 32	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)
		RCA maximum dose (cGy)	263 ± 73	259 ± 34	218 ± 37	$P<0.001$* ($P<0.001^{\ddagger\ddagger, \ddagger\ddagger\ddagger}$)

Number in "patient" indicates number of patient. Number with "±" indicates mean with standard deviation.
*, Kruskal-Wallis test; $\ddagger$, W vs W-FIF; $\ddagger\ddagger$, W vs FIF; $\ddagger\ddagger\ddagger$, W-FIF vs FIF for Scheffe's method of Kruskal-Wallis test, respectively.
W, wedge method; W-FIF, wedge field-in-field method; FIF, field-in-field method; PTV, planning target volume; NS, not significant; BPe, breast PTV evaluation; ALN, axillary lymph node; OAR, organ at risk; ip, ipsilateral pulmonary; LAD, left anterior descending coronary artery; CCA, left circumflex coronary artery; RCA, right coronary artery.

stream method accounting for 39% of all radiotherapy treatments, while the physical wedge method was reported to account for 29% and the dynamic wedge method for 28% of radiotherapy treatments; thus, further spread of FIF is desirable. Ratosa *et al.* stated that it is unclear whether a slight improvement in dosimetric parameters resulting from irradiation studies could reduce the incidence of clinically significant adverse events [13]. Further studies are needed to examine the relationship between the results of dosimetry parameters and the occurrence of adverse events due to differences in irradiation methods.

In this retrospective study, almost all patients who were treated in our hospital were analyzed by each irradiation method used sequentially for each era. The limitation of this approach is that the bias of background factors for each group does not completely disappear; however, this bias of background factors might have been reduced by the large number of cases, which exceeded 500.

In conclusion, one of the key factors affecting dose distribution in breast cancer radiotherapy is the treated breast volume. In the current study, we examined irradiation methods according to breast volume in Asian breast cancer patients, and compared the results with those in European and North American patients with larger breast volumes. Our results revealed that FIF is less affected by breast volume than conventional irradiation methods such as W, and contributes to the uniformity of dose distribution for breasts of any size.

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