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ORIGINAL ARTICLE

Comparison of hypofractionated and conventionally fractionated whole-breast irradiation for early breast cancer patients: a single-institute study of 1,098 patients

Kumiko Karasawa · Hiroaki Kunogi · Takahisa Hirai · Hidehiro Hojo · Hisako Hirowatari · Hiromi Izawa · Kana Ito · Keisuke Sasai · Motohiro Kawashima · Tomohisa Furuya · Satoru Sugimoto · Chie Kurokawa · Shuichi Ozawa · Mitsue Saito

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Abstract
Purpose To evaluate the efficacy and safety of hypofractionated whole-breast irradiation (HF-WBI) compared with conventionally fractionated (CF) WBI.
Materials and methods Patients with early breast cancer (stages 0–II and <3 positive lymph nodes) who had undergone breast-conserving surgery were eligible for the HF-WBI study. HF-WBI was administered at 43.2 Gy in 16 fractions over 3.2 weeks to the whole breast with an additional tumor-bed boost of 8.1 Gy in 3 fractions over 3 days for positive surgical margins or those <5 mm. CF-WBI was administered at 50 Gy in 25 fractions over 5 weeks to the whole breast with an additional tumor-bed boost of 16 Gy in 8 fractions over 1.4 weeks to 6 Gy in 3 fractions over 3 days, depending on margin status.
Results From April 1, 2006, to December 31, 2010, 717 patients were registered and 734 breasts were treated by HF-WBI. In the same period, 381 patients and 393 breasts who matched the study criteria chose CF-WBI, so the total number of patients in this comparison was 1,098. Grade 2 acute skin reactions were observed for 24 patients (3 %) in the HF-WBI group and 53 patients (14 %) in the CF-WBI ($p < 0.001$) group. The median follow-up period was 27 months. Two cases of intrabreast tumor recurrence were observed in each treatment group. Regional lymph node recurrence was observed in 1 HF-WBI patient and 2 CF-WBI patients.
Conclusion HF-WBI is superior to CF-WBI in terms of acute skin reaction and has the same short-term efficacy.

Keywords Early breast cancer · Whole-breast irradiation · Hypofractionated radiotherapy · Acute adverse effects · Conventionally fractionated radiotherapy

Introduction

Breast-conserving therapy (BCT) consists of partial mastectomy and whole-breast irradiation (WBI), which is performed after BCT as part of standard care in early breast cancer. Conventional WBI involves administration of 50 Gy in 25 fractions over 5 weeks to the whole breast, with additional tumor-bed boosts [1]. Several meta-analyses have proved the usefulness of conventionally fractionated (CF) WBI [2–10]. However, CF-WBI requires an irradiation period of 5 weeks or more, which is inconvenient for patients, institutes, and systemic treatment schedules. As a result, hypofractionated (HF) WBI has been gaining acceptance in practice. In addition, many studies report equal effectiveness and safety of HF-WBI and CF-WBI [2–10]. The purpose of this clinical trial was to evaluate the efficacy, safety, and convenience of HF-WBI compared with CF-WBI.

K. Karasawa · H. Kunogi · T. Hirai · H. Hojo · H. Hirowatari · H. Izawa · K. Ito · K. Sasai · T. Furuya
Department of Radiology, Faculty of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

K. Karasawa · K. Ito · M. Kawashima · T. Furuya · S. Sugimoto · C. Kurokawa · S. Ozawa
Department of Medical Physics for Advanced Radiotherapy, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

K. Karasawa (✉)
Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba, Chiba 263-8555, Japan
e-mail: kkarasaw@nirs.go.jp

M. Saito
Department of Breast Surgery, Faculty of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Three years from the beginning of our study, we found the severity of skin reaction was different in the two groups. We checked breast skin dose by skin-dose film dosimetry with radiochromic film and calculated the biologically effective dose (BED) for investigation of the different skin reaction.

Materials and methods

Protocol

We submitted the HF-WBI study protocol to Juntendo University Hospital's Institutional Review Board (IRB) in January 2006, and received study approval in March 2006. The IRB commented that there was not enough evidence for HF-WBI in Japan and we needed to conduct a phase II study before a phase III randomization study of HF-WBI and CF-WBI. We therefore redesigned the HF-WBI study from phase III to phase II and compared the results with those for patients who did not participate in the study and were treated by CF-WBI. We explained to all patients who matched the HF-WBI study criteria that there was some evidence in other countries but not enough evidence for HF-WBI in Japan, and explained the details of HF-WBI and CF-WBI. Patients who were willing to participate in the clinical trial were irradiated by HF-WBI and those who were not willing to participate in the study were irradiated by CF-WBI. Written informed consent was obtained from all patients.

Patients with early breast cancer stages 0–II and <3 positive lymph nodes who had undergone partial mastectomy with sentinel lymph node biopsy or axillary node dissection were eligible for this study. Staging procedure and pre-operative examination consisted of general blood test, tumor markers, mammography, ultrasound of breast and regional lymph node area, breast MRI, tumor biopsy, and CT scan of neck to pelvis. Post-operative pathological examination consisted of pathological type, tumor extension, marginal status, estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor related 2 (Her2), and pathological status of lymph nodes. Exclusion criteria of this study included any active collagen disease, active double primary cancer, concurrent chemotherapy, previous chest irradiation, patients who needed irradiation of regional lymph node area and pregnancy.

To determine the HF-WBI fractionation schedule, data from the Ontario trial [5] were utilized. HF-WBI involved 43.2 Gy in 16 fractions over 3.2 weeks to the whole breast with an additional tumor-bed boost of 8.1 Gy in 3 fractions over 3 days for cases with positive surgical margins or those <5 mm. Margin criteria were defined as follows:

- positive or close, tumor cells at or within 5 mm of the tumor cell-free margin;
- negative, tumor cells at or beyond 5 mm of the free margin.

CF-WBI involved 50 Gy in 25 fractions over 5 weeks to the whole breast with an additional tumor-bed boost of 6 Gy in 3 fractions over 3 days for cases with negative surgical margins, 10 Gy in 5 fractions over 5 days for cases with positive surgical margins or those within 5 mm of the tumor cell-free margin, or 16 Gy in 8 fractions over 1.4 weeks for cases with positive surgical margins or for cases with more than 3 marginal ducts. This is the standard of care at our institution.

Radiotherapy for all the patients was planned using the Eclipse three-dimensional treatment-planning system (Varian Medical Systems, Palo Alto, CA, USA). To facilitate treatment planning, computed tomography of the chest was obtained with each patient in the upright position, and the body outline, left and right lungs, and heart appeared to be delineated. The clinical target volume (CTV) was defined as the entire palpable breast. The planning target volume (PTV) was obtained by adding a 10-mm margin to the CTV and an additional 15-mm margin for the skin. The WBI treatment technique involved the use of 2 opposing tangential fields. Radiation fields were customized as appropriate by a multileaf collimator. To minimize irradiation of the lungs, the angle of the beams was adjusted to the inner margin. Electronic tissue compensation planning was performed by use of the Eclipse software to ensure uniform dose distribution and to achieve target dose homogeneity within ±7 % of PTV. All breasts were irradiated with 4-MV photon beams (Clinac 21EX; Varian). Tumor-bed boosts were given using 9–15-MeV electrons; field size and electron energy depended on the area which needed to be irradiated, the thickness of breast tissue at the boost site, and tumor depth from the skin.

The primary endpoint was intrabreast tumor control (IBTC). Secondary endpoints were acute adverse effects of the skin, subcutaneous tissue, breast tissue, and lungs, and late adverse effects of the skin, subcutaneous tissue, breast tissue, lungs, ribs, and heart. Acute adverse effects were investigated weekly during treatment and 1 or 2 weeks after completion of treatment. They were scored according to common terminology criteria for adverse events (CTCAE) v 3.0. Late adverse effects and tumor control were assessed at every clinical visit and at least every 6 months after completion of treatment. Late adverse effects were scored on the late effects normal tissue—subjective, objective, management, analytic (LENT-SOMA) scale.

Film dosimetry

Three years from the beginning of study we found the severity of skin reaction was different in the two groups. In 2009 we checked the skin dose for some patients by use of radiochromic films. At that time we did not find any skin dose differences. We therefore decided to evaluate the real skin dose and skin reaction. We submitted a skin dosimetry study protocol to the IRB in April 2011 and it was approved in June 2011. We checked breast skin dose at three points by skin dose film dosimetry, by use of radiochromic film, and calculated the BED to investigate skin reaction differences. Dosimetry was performed by use of the GAFCHROMIC EBT (International Specialty Products, Wayne, NJ, USA). Dosimetric points were:

- point 1, 5 cm away from the nipple in the inner lower quadrant;
- point 2, 5 cm away from the nipple in the outer upper quadrant; and
- point 3, just above the nipple.

Skin doses were measured for 10 patients undergoing HF-WBI and 8 patients undergoing CF-WBI. Fractionation tissue sensitivity was quantified by use of the α/β ratio and linear-quadratic formula $E/\alpha = nd(1 + d/\alpha/\beta)$ to calculate the isoeffect. Acute skin reactions to radiation have an α/β ratio of 10.6 Gy [11].

Statistical analysis

The chi-squared test and Fisher's exact test were used to compare results for the 2 treatment groups. Associations of early toxicity with menopausal status, irradiation technique, concurrent endocrine therapy, and previous chemotherapy were analyzed for the 2 treatment groups by use of the chi-squared test and a logistic regression model. IBTC was calculated by use of the Kaplan–Meier method and the 2 treatment groups were compared by use of the log rank test. Cox's proportional hazards regression model was adjusted to obtain the hazard ratio. A p value of <0.05 was considered to be statistically significant. Statistical analysis was performed by use of the SAS package version 8.02 (SAS Institute, Cary, NC, USA).

Results

Patients

From April 1, 2006, to December 31, 2010, 717 patients who matched in the eligibility criteria for HF-WBI were registered and 734 breasts were treated. The number of control CF-WBI patients was 381, and 393 breasts were treated (Tables 1, 2). The 1,127 breast tumors were categorized into the following T stages: Tis ($n = 191$), T1 ($n = 599$), and T2 ($n = 337$). One hundred and fifty-two tumors were N1 (Table 2). Clinical stages were: stage 0 ($n = 191$), stage I ($n = 543$), stage IIa ($n = 301$), and stage IIb ($n = 92$). The age of the patients ranged from 22

Table 1 Patient characteristics (total no. of participants 1,098)

Characteristics	HF-WBI	CF-WBI
Total no. of patients	717 (65 %)	381 (35 %)
Age (years) (median)	29–85 (54)	22–88 (53)
Menopause	417 (58.2 %)	213 (55.9 %)
Bilateral tumor	17 (2.4 %)	12 (3.1 %)
Neo-adjuvant chemo.	238 (33.2 %)	86 (22.6 %)
Concurrent endo.	88 (12.3 %)	56 (14.7 %)
Adjuvant therapy	426 (59.4 %)	195 (51.2 %)

chemo chemotherapy, *endo* endocrine therapy

Table 2 Tumor characteristics (total no. of tumors 1,127)

Characteristics	HF-WBI	CF-WBI
No. of breasts	734	393
T stage		
Tis	102 (13.9 %[a])	89 (22.6 %)
T1	388 (52.9 %)	211 (53.8 %)
T2	244 (33.2 %)	93 (23.6 %)
N stage		
N0	635 (86.5 %)	340 (86.3 %)
N1	99 (13.5 %)	53 (15.9 %)
Pathology		
DCIS	102	89
IDC	598	284
Other	34	20
ER status		
Positive	577 (78.6 %)	319 (81.2 %)
Negative	151	70
Unknown	6	4
PgR status		
Positive	483 (65.8 %)	274 (69.8 %)
Negative	243	115
Unknown	8	4
HER2 status[b]		
Positive	136 (21.5 %)	64 (21.1 %)
Negative	494	238
Unknown	2	2
Left sided tumor	358 (48.8 %)	196 (49.9 %)
Positive or close margin	236 (32.2 %)	156 (39.7 %)

[a] Patients were informed about the lack of evidence of the efficacy of HF-WBI in Tis

[b] In invasive tumor (exclude DCIS)

to 88 years. No significant differences were found between the 2 groups in terms of age, menopausal status, T1, N1, tumor side (left or right breast), bilateral tumor, ER, PgR, Her 2 status or concurrent endocrine therapy. However, use of neo-adjuvant chemotherapy (HF-WBI group 33.2 % vs. CF-WBI group 22.6 %) and incidence of stage T2 (HF-WBI group 33.2 % vs. CF-WBI group 23.6 %) were significantly different. Incidence of ductal carcinoma in situ (DCIS, Tis) was significantly lower in the HF-WBI group (13.9 vs. 22.6 % in the CF-WBI group). This was because patients had been informed there was less evidence of the efficacy and safety of HF-WBI in DCIS. Tumor margins were positive or close for 32.2 % of patients in the HF-WBI group and 39.7 % of patients in the CF-WBI group.

Convenience

Treatment was administered for 21–36 days (median 26 days) in the HF-WBI group and for 38–49 days (median 43 days) in the CF-WBI group. In Japanese health insurance, treatment management fee and external beam irradiation fee per fraction depend on treatment method. We assessed our technique as moving field irradiation. Treatment costs for HF-WBI were 252,800 yen (US$3,224 at 1 US$ = 78 yen) in cases with negative margins and 281,600 yen (US$3,591) in cases with positive margins (3 times electron boost). Treatment costs for CF-WBI were 423,800 yen (US$5,405) in cases with negative margins and 443,000 yen (US$5,649) in cases with positive margins. In cases of bilateral tumor, Japanese health insurance calculates the second site at half-price. For HF-WBI of 16 fractions add 144,000 yen (US$1,836), for CF-WBI of 25 fraction add 225,000 yen (US$2,869), and for tumor-bed boost in 3 fractions add 12,600 yen (US$161) to the first site price. For example, in cases with negative margins in both sides, the total treatment cost is 396,800 yen (US$5,061) in HF-WBI and 648,800 yen (US$8,276) in CF-WBI. Thus, treatment duration and costs were almost one-third lower for HF-WBI for all patients.

Acute adverse effects

Grade 2 acute skin reactions were observed in 24 patients (3.3 %) from the HF-WBI group and 53 patients (13.5 %) from the CF-WBI group (Table 3). Incidence of other grade 2 effects, mastitis and pneumonitis, was almost the same in two groups.

Factors associated with grade 2 dermatitis are provided in Table 4. Fractionation schedule was the most significant factor ($p < 0.001$ in univariate and multivariate analysis) and menopausal status was a marginally significant factor ($p < 0.05$ in univariate analysis, $p = 0.04$ in multivariate analysis).

Table 3 Acute adverse effects

	Grade	HF-WBI	CF-WBI
Skin reaction	0	183	33
	1	529	308
	2	24 (3.3 %)	53 (13.5 %)
Mastitis (soft tissue, others)	2	3 (0.4 %)	1 (0.3 %)
Pneumonitis	2	2 (0.3 %)	2 (0.5 %)

Scored according to the common terminology criteria for adverse events (CTCAE) v 3.0

Table 4 Factors associated with grade 2 dermatitis

Variable	No. (%)	χ^2	Univariate (p)	Multivariate (p)
HF-WBI	3.3	41.97	<0.001	<0.001
CF-WBI	13.5			
Menopause	6.7	4.850	<0.05	0.04
Premenopause	7.2			
Bilateral	11.1	0.029	NS	NS
Unilateral	6.7			
Neo-adj. chemo.	5.7	0.882	NS	NS
No chemo.	7.3			
Conc. endo.	5.9	0.411	NS	NS
No endo.	7.5			

chemo chemotherapy, *endo* endocrine therapy

Table 5 Results of film dosimetry

Arm	Isocenter dose	Average dose		
		Point 1	Point 2	Point 3
Dose ratio				
HF ($n = 10$)	270	164	161	138
CF ($n = 8$)	200	106	112	93
CF/HF	1.35	1.34	1.36	1.35
BED difference				
HF dose		26.2 Gy/16 f	25.8 Gy/16 f	22.1 Gy/16 f
HF-BED	$\alpha/\beta = 10.6$	30.3	29.7	25.0
CF dose		26.5 Gy/25 f	28.0 Gy/25 f	23.3 Gy/25 f
CF-BED	$\alpha/\beta = 10.6$	29.7	31.0	25.3
BED difference		0.6	1.3	0.3
		HF > CF	CF > HF	CF > HF

Biologically effective dose (BED) = $E/\alpha = nd(1 + d/\alpha/\beta)$

The average skin dose, dose ratios, and BED differences for the 10 HF-WBI patients and 8 CF-WBI patients at points 1, 2, and 3 are shown in Table 5. In the same way as the isocenter dose of 2.7 Gy was 1.35 times higher than 2.0 Gy, skin dose at points 1, 2, and 3 were 1.34, 1.36, and

1.35 times higher, respectively. Average BED at points 1, 2, and 3 were 30.3, 29.7, and 25.0, respectively, in HF-WBI patients and 29.7, 31.0, and 25.3, respectively, in CF-WBI patients. BED differences at points 1, 2, and 3 were just 0.6, 1.3 and 0.3, respectively. There were no significant differences between the two groups with regard to dose ratio and BED.

Radiation pneumonitis was observed in 2 patients (0.3 %) from the HF-WBI group and in 2 patients (0.5 %) from the CF-WBI group. No organizing pneumonia was observed. No other late adverse effect above grade 2 was observed in either group.

Tumor control

The follow-up period ranged from 8 to 64 months with a median of 27 months. Two cases of intrabreast tumor recurrence (IBTR) were observed in each treatment group (Table 6). The IBTC was 99.7 % in the HF-WBI group and 99.5 % in the CF-WBI group. Surgical margins were positive for all IBTR patients. Margin status was significantly associated with IBTR ($p < 0.01$). Radiation schedule and other factors had no effect on IBTR in this period.

Regional lymph node recurrence was observed in 1 patient from the HF-WBI group and 2 patients from the CF-WBI group. Distant metastasis was observed in 8 patients from the HF-WBI group and 3 patients from the CF-WBI group. Mortality from breast cancer occurred for 3 patients in the HF-WBI group.

Discussion

BCT is a standard treatment in early breast cancer. The major benefit of BCT is preservation of the breast, with all the consequent advantages in respect of the patients' quality of life. In recent years, the amount of surgery has been decreasing, because of advances in diagnostic precision and the extensive use of systemic therapy. However, the 5 to 7-week schedule of CF-WBI used in BCT places a burden on both the patients' quality of life and on radiotherapy departments that receive a large number of breast cancer patients. HF-WBI is one solution used to improve this situation. HF-WBI has been performed for more than 20 years in the UK and other countries influenced by British medical practice. Six randomized trials and more than 30 nonrandomized trials [2–10] of HF-WBI have reported tumor control and damage to normal tissue similar to those for the standard CF-WBI schedule of 50 Gy in 25 fractions over 5 weeks.

Table 6 Intrabreast tumor recurrence cases

	Case 1	Case 2	Case 3	Case 4
Method	HF	HF	CF	CF
Age	44	57	59	51
Stage	TisN0M0	T2N1M0	T1N0M0	TisN0M0
ER	Positive	Negative	Positive	Positive
PgR	Positive	Negative	Positive	Positive
HER2	–	Positive	Positive	–
Dose (Gy)	51.3	54	60	60
Margin	Positive	Positive	Positive	Positive
Rec. period (months)	36	22	24	36
Rec. path.	DCIS	IDC	DCIS	IDC
Treatment	Mastec	Chemo	Mastec	Mastec

HF HF-WBI, *CF* CF-WBI, *ER* estrogen receptor, *PgR* progesterone receptor, *Rec* recurrence, *path.* pathology, *Mastec* mastectomy

The American Society of Radiation Oncology (ASTRO) consensus guideline for HF-WBI [2] states that patients suitable for HF-WBI are those with stage I breast cancer (T1N0M0), favorable histology, and negative surgical margins who are ER-positive and HER2-negative. Our prospective study was a nonrandomized, single-institute study of 2 radiotherapy fractionation schedules for 1,098 patients. One-thousand one-hundred and twenty-seven breasts were irradiated over a period of 5.9 years. Seven-hundred and seventeen (65 %) patients selected HF-WBI as their preferred treatment. At the beginning of the trial, almost the same number of patients chose HF and CF, but the number of HF patients gradually began to increase as a result of breast oncologists' and former patients advising its use because of its convenience and the low occurrence of acute skin reactions. In the HF-WBI group, 102 patients with DCIS, 244 with T2, 236 with positive or close surgical margins, and 151 with ER-negative status, and 136 with HER2-positive status were included. IBTR was recognized in 2 patients in the HF-WBI group—1 case was Tis with ER-positive status and the other was T2 with HER2-positive status. Of the 2 patients with IBTR in the CF-WBI group one was Tis with ER-positive status and the other was T1 with HER2-positive statusd. IBTC in this study was >99 % in both treatment groups. All of the IBTR cases had positive surgical margins (Table 6). The factor that affected IBTR was margin status. However, with median follow up of 27 months, it is too early to discuss tumor control and affected factors. Distant metastases were significantly higher in the HF-WBI group, possibly because the incidence of T2 cancer was higher in HF-WBI group. Longer follow-up is necessary to determine the final outcome.

PTV dose homogeneity and normal tissue dose reduction are more important in HF-WBI than in CF-WBI. In HF-WBI, three-dimensional intensity-modulated radiation therapy (IMRT) is more appropriate than an open field or a physical wedge filter. Use of an electric compensator or the field-within-a-field technique is easier and results in good dose homogeneity as IMRT. The Eclipse software used in

this study ensured adequate electronic tissue compensation and good dose homogeneity. The total planning time using the Eclipse software was less than 1 h.

Most HF-WBI randomized trials have required the maximum dose to the breast on the central axis plane to be no greater than 105–107 % and no less than 93–95 % of the prescription dose [2]. No stipulations were placed on the homogeneity of dose distribution outside the central axis plane. Most patients in these trials were treated by use of two-dimensional planning techniques without tissue heterogeneity corrections. Optimizing the homogeneity of dose in the off-axis planes and in the central-axis plane reduces acute toxicity. Some studies have reported a correlation between skin reaction and breast volume and one Egyptian study reported a significant correlation between breast volume and the severity of acute skin reactions [12]. This, however, was mainly caused by inhomogeneous distribution of the dose to large-volume breasts by the conventional irradiation technique. In our study with Japanese patients, the number of patients was large enough to eliminate breast volume bias and we used a dose homogeneity-correction technique within the whole PTV. The ASTRO guideline recommends that the minimum dose should be no less than 93 % and that the maximum dose should be no more than 107 % of the prescription dose (±7 %) in the central-axis plane, and also encourages the use of three-dimensional planning techniques for all patients to minimize dose inhomogeneity and reduce toxicity [2].

In our study the percentage of grade 2 acute skin reactions was significantly lower in the HF-WBI group (3.3 %) than in the CF-WBI group (13.5 %; Tables 3, 4). START trials have reported less acute reactions with HF-WBI [9, 10]. The START A trial reported that severe acute reactions were 0.3 % in the 50 Gy arm, 0 % in the 41.6 Gy arm, and 0 % in the 39 % arm (>0.005) [9]. In a retrospective study from the Cancer Institute of the Japanese Foundation for Cancer Research, 9 % of patients in the HF-WBI group (40 Gy in 16 fractions) and 22 % in the CF-WBI group suffered grade 2–3 dermatitis ($p = 0.016$) [13]. Differences between radiation techniques affect skin dose and reaction. Therefore, skin-dose film dosimetry was performed to evaluate skin dose for the 2 treatment groups in our study. However, we found no significant differences of skin dose and BED in the two groups. Thus, we believe skin dose and BED do not correlate simply with skin reaction. Skin reaction might be affected by volume and type of the low-energy X-ray component, and scattered radiation from the multileaf collimator, wedge filter, and other devices. We could not identify a clear reason for the different skin reactions between the 2 groups from this dosimetry. We believe the modern radiation technique to improve PTV dose homogeneity could be affecting skin reaction, or radiobiological uncertainties in skin reaction may exist that are not reflected in the α/β ratio.

The incidence of pneumonitis in both treatment groups was lower than that in other studies. Careful field settings of the inner margin to minimize irradiation to the lungs and use of the Eclipse software for electronic tissue compensation planning contributed to this result. No changes in breast appearance were reported during the follow-up period. No other late adverse effects above grade 2 were observed in either treatment group. However, patients are still being carefully monitored at the time of writing of this manuscript because of the possibility of higher incidence of late adverse effects in the breast, heart, lungs, and brachial plexus in the HF-WBI group.

Conclusion

In this study we compared treatment results for 717 patients and 734 breasts treated by HF-WBI with those for 381 patients and 393 breasts treated with CF-WBI who matched the eligibility criteria of the HF-WBI clinical study. Incidence of acute skin reactions was significantly lower in HF-WBI group. IBTC was 99 % in both groups, with no difference during the median 27-month period of follow up. Cost and treatment period for HF-WBI were two-thirds those for CF-WBI. If acute skin reaction in other studies which use the dose homogeneity technique for the whole PTV is as low as ours, the patient burden of WBI would be reduced further. Our study included ER-negative, HER2-positive, and surgical margin-positive patients. This is the first report to compare the efficacy, safety, and convenience of HF-WBI and CF-WBI for Japanese patients, and this group of patients will provide much information with longer follow up.

Conflict of interest The authors report no conflict of interest or financial support for this study.

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