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A primary analysis of a multicenter, prospective, single-arm, confirmatory trial of hypofractionated whole breast irradiation after breast-conserving surgery in Japan: JCOG0906

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Abstract

Objective: To evaluate the safety of hypofractionated whole breast irradiation in Japanese women after breast-conserving surgery.

Methods: Japanese women who had invasive breast cancer with a clinical tumor size ≤3 cm, pN0-1c and a negative inked margin were enrolled. Hypofractionated whole breast irradiation (42.56 Gy/16 fractions) was delivered, adding boost irradiation (10.64 Gy/4 fractions) when the surgical margin was ≤5 mm. The treatment course was meant to be completed within 29 days or 33 days (plus boost irradiation). The primary endpoint was the proportion of grade ≥2 of pre-specified late adverse reactions, including telangiectasia, ulceration, fibrosis, fracture, pneumonitis, cardiac ischemia/infarction, pericardial effusion and breast pain, within 3 years. A sample size of 310 patients was set, with one-sided alpha of 0.05, beta of 0.1, threshold value of 8% and expected value of 4%. Secondary endpoints included the proportion of treatment completion within the recommended period and early adverse events within 90 days. Adverse events/adverse reactions were evaluated using CTCAE-3.0.

Results: Between 2010 and 2012, 312 women were enrolled; 306 received hypofractionated whole breast irradiation, but 6 chose conventional fractionated WBI, with 301 patients (96.5%) treated within the recommended period. Grade 2 early adverse events were found in 38 patients (12.4%); none had grade 3/4. Among the 303 evaluable patients, 13 (4.3%; 90% CI 2.6–6.7) had grade 2/3 late adverse reactions, including one with grade 3 pneumonitis, which was under the threshold value.

Conclusion: Hypofractionated whole breast irradiation is considered to be safe and one of the standard treatments for Japanese women with margin-negative invasive breast cancer after breast-conserving surgery.

Key words: early breast cancer, breast-conserving therapy, hypofractionated whole breast irradiation, late adverse reaction

Introduction

Breast-conserving therapy involving breast-conserving surgery (BCS) and radiation therapy is the treatment of choice for many women with early-stage breast cancer. With regard to radiation volume, dosing and scheduling after BCS, standard treatment is commonly delivered to the whole breast (with or without regional lymph nodes) in 1.8–2 Gy daily conventional fractions over 5–7 weeks, to achieve a total dose of 45–50 Gy (1). However, several randomized trials showed that shorter hypofractionated whole breast irradiation (HF-WBI) achieved comparable results to conventional fractionated whole breast irradiation (CF-WBI) (2–9). Shorter schedules with HF-WBI could be a reasonable and beneficial alternative after BCS for some women, reducing their socio-economic burden during radiation treatment periods by reducing visiting times to hospitals and medical expenses. Moreover, shorter HF-WBI may be particularly beneficial in Japan where rapidly growing demand for radiation therapy is placing pressure on limited institutional resources for radiation therapy. Therefore, the number of patients and radiation oncologists who choose shorter HF-WBI over CF-WBI has been growing in Japan.

Whereas favorable outcomes have been reported from Western countries (2–9), there has been only a small amount of evidence from a few single-institute studies of the safety and efficacy of HF-WBI after BCS for Japanese women with early-stage breast cancer, although they reported favorable outcomes on Japanese women who underwent HF-WBI (10–12). Since there are obvious differences in physique between women in Japan and those in Western countries, and since radiation dose distribution largely depends on the size and shape of the breast, particular care is needed when interpreting results from Western countries. Because using a large fraction dose may enhance late radiation damage to normal tissue, the safety of this new approach must be addressed before introducing it into Japanese daily clinical practice. Thus, a prospective single-arm confirmatory trial (Radiation Therapy Study Group, Japan Clinical Oncology Group: JCOG0906, UMIN Clinical Trials Registry: UMIN000003200) was conducted. This is the first report describing the primary analysis of this clinical trial.

Materials and methods

Patients

Patients eligible for enrollment were Japanese women, aged between 20 and 75 years, underwent BCS and able to give written informed consent. Preoperative eligibility criteria included: (i) clinical tumor size ≤3 cm on ultrasound; (ii) no evidence of multiple tumors on mammography; (iii) no lung metastasis on chest X-ray; (iv) no preoperative systemic therapy and (v) no distant metastasis. Operative eligibility criteria included: (i) partial lumpectomy or quadrantectomy with sentinel lymph node biopsy or axial lymph node dissection of levels I and II; (ii) no endoscopic operation; (iii) no concurrent breast reconstruction and (iv) no ongoing treatments for postoperative complications. Pathological eligibility criteria included: (i) invasive carcinoma; (ii) pathologically N0-N1c; (iii) pathologically negative inked margin and (iv) no multi-centric carcinoma. Postoperative treatment included systemic chemotherapy for patients with ER/PgR/HER2-negative breast cancer, endocrine therapy for patients with ER/PgR-positive breast cancer or anti-HER2 therapy for patients with HER2-positive breast cancer. If indicated, chemotherapy was to be completed before enrollment. Concurrent chemotherapy and anti-HER2 therapy were not acceptable during radiation therapy. If indicated, endocrine therapy might continue during radiation therapy. Exclusion criteria included any other concomitant active malignancy, uncontrolled diabetes, active interstitial pneumonitis or lung fibrosis, active collagen disease, heart failure, myocardial infarction or angina pectoris within 6 months, pregnancy or nursing, major mental disease and prior overlapping radiation. Figure 1 shows the trial's schema including eligibility criteria. This study protocol was approved by the institutional review board of each participating hospital.

Treatment methods

The patients were positioned supine with the arm abducted. The treatment volume included the whole breast, exclusive of axillary and internal mammary regions. A daily dose of 2.66 Gy in five weekly fractions was delivered to the whole breast with two tangential opposed portals, using 4- or 6-MV X-rays. When the surgical margin was ≤5 mm, boost irradiation (BI) of 10.64 Gy in four

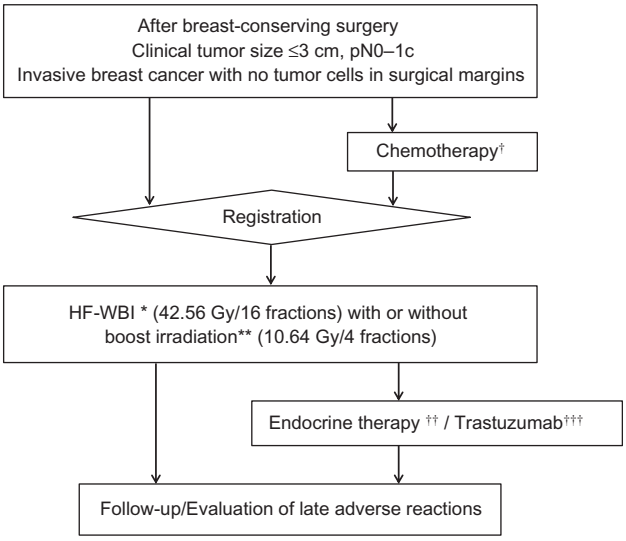

Figure 1. Trial's schema. *HF-WBI: hypofractionated whole-breast irradiation; **Boost irradiation added when the surgical margin was ≤5 mm; †Systemic chemotherapy for patients with ER/PgR/HER2-negative breast cancer was to be completed prior to enrollment, if indicated; ††Endocrine therapy for patients with ER/PgR-positive breast cancer might continue during radiation therapy, if indicated; †††Anti-HER2 therapy for patients with HER2-positive breast cancer was not acceptable during radiation therapy, if indicated.

fractions was added to the original tumor bed with a 2.0-cm margin, using electrons with an energy range of 6–13 MeV or X-rays of 4 or 6 MV. The treatment course was to be completed within 29 days (HF-WBI) or 33 days (HF-WBI plus BI) from the start of radiation therapy. Prescription doses for the whole breast were calculated to an isocenter of the central axis in the treatment volume. Wedges or compensating filters were used to achieve a uniform dose distribution ranging from 95% to 110% in the breast. The central lung distance (CLD) in a central axis plane and the maximum heart distance (defined as the maximum distance of the heart contour, as seen in a beam's eye view of the medial tangential fields, to the medial field edge) were recommended to be within 3.0 and 1.0 cm, respectively, unless shielding a tumor bed.

Endpoints and assessment methods

The primary endpoint was the proportion of eight pre-specified late ARs of grade ≥2, which could be related to treatment, occurring between 91 days and 3 years from the start of HF-WBI. The pre-specified items included well-known important late adverse reactions (ARs) which were related to treatment: telangiectasia of the skin; skin ulceration; fibrosis of the deep connective tissue; rib fracture; pneumonitis; cardiac ischemia/infarction; pericardial effusion and breast pain. These items were chosen in accordance with those evaluated in the pilot survey conducted to determine the expected value of this study, which included 703 patients and found 29 late ARs of grade 2 or 3 in 27 patients (3.8%), with events including breast pain, telangiectasia of the skin, skin ulceration, fibrosis of the deep connective tissue, rib fracture and pneumonitis (13). Late ARs were evaluated every 2 months for the first 6 months, every 6 months between 6 months and 3 years, and every year between 3 and 5 years by interview, inspection and palpation using CTCAE version 3.0. Those who were followed for at least 2.5 years without grade ≥2 late ARs or who were not even followed for 2.5 years but had grade ≥2 late ARs were included in the analysis.

Secondary endpoints included the proportion of treatment completion within the recommended period, early adverse events (AEs), which included all events regardless of relation to treatment occurring within 90 days from the start of HF-WBI, overall survival (OS), disease-free survival (DFS), ipsilateral-breast relapse-free survival (IBRFS) and the proportion of breast cosmetic change. Early AEs were evaluated every week during radiation therapy using CTCAE version 3.0. All patients were examined by mammography every year.

Statistical analysis

To analyze the proportion of pre-specified late ARs of grade ≥2, the sample size was set as 310 patients with one-sided alpha of 0.05, beta of 0.1, threshold value of 8% and expected value of 4%, which were determined in reference to the pilot survey (13). Analyses were done with all treated patients.

Confidence intervals (CIs) of the proportion of ARs and treatment completion were calculated by the Clopper–Pearson method. All statistical analyses were performed using SAS, release 9.2 (SAS Institute, Cary, NC, USA).

Results

Between February 2010 and August 2012, 312 patients were enrolled from 25 hospitals in Japan, all of whom were eligible. Table 1 shows the patients' characteristics. A total of 306 received HF-WBI, while 6 chose CF-WBI prior to the start of irradiation. Therefore, 306 patients were included in the efficacy and safety analysis. HF-WBI without BI was received by 240 patients, 2 of whom converted to CF-WBI. Sixty-six patients received HF-WBI plus BI. Figure 2 shows the patient flow diagram.

Table 1 Patients' characteristics ($n = 312$)

Characteristic		$n = 312$
Age, years	Median (range)	56 (32–75)
Performance status	0/1	308/4
Tumor site	Right/left	169/143
Surgery of lymph nodes		
Sentinel lymph node biopsy		243
Level I sampling		10
Level II dissection		17
Level I + II + (α) dissection		42
Pathological tumor size, cm	Median (range)	1.5 (0.1–4.0)
Histological subtype		
Invasive ductal carcinoma		291
Others		21
pTNM		
T1mi/T1a/T1b/T1c/T2		1/22/75/154/60
N0/N1mi/N1a		271/4/37
I/IIA/IIB		228/68/16
Status of surgical margin		
No cancer cells		245
Positive within 5 mm or less		67
Nuclear grade	1/2/3/Missing	159/64/82/7
Biological status		
ER	Negative/positive	31/281
PgR	Negative/positive	72/240
HER2/neu	0/1+/2+/3+/Missing	130/142/24/13/3
Adjuvant therapy	Yes/no	190/122
Endocrine therapy	Yes/no	128/62
Anthracycline	Yes/no	67/123
Taxane	Yes/no	50/140
Trastuzumab	Yes/no	5/185

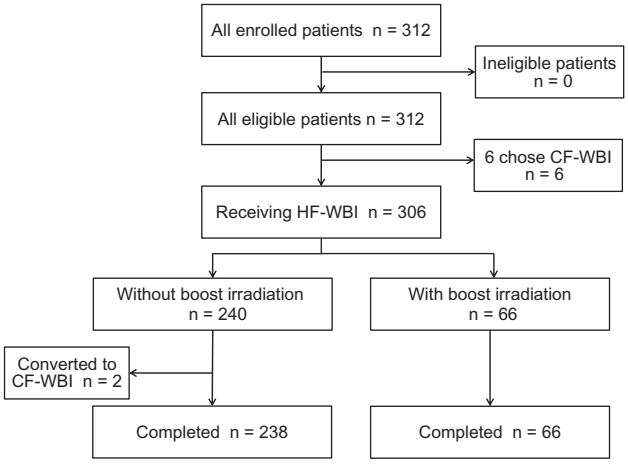

Figure 2. Patient flow diagram. A total of 312 patients were enrolled between February 2010 and August 2012. No patients were ineligible. However, six chose CF-WBI prior to the start of irradiation. Among 240 without boost irradiation, two refused HF-WBI and converted to CF-WBI. 304 completed HF-WBI with or without boost irradiation and were followed up. CF-WBI: conventional fractionated whole-breast irradiation, HF-WBI: hypofractionated whole-breast irradiation.

Table 2 Highest score of acute AEs evaluated by CTCAE v3.0, occurring during 90 days from the start of HF-WBI

AE	Grade 1 (%) $n = 306$	Grade 2 (%) $n = 306$
Radiation dermatitis	236 (77.1)	25 (8.2)
Skin pigmentation	192 (62.7)	2 (0.7)
Skin depigmentation	5 (1.6)	0 (0)
Itchiness	69 (22.5)	2 (0.7)
Dry skin	84 (27.5)	2 (0.7)
Pain breast	112 (36.6)	2 (0.7)
Skin	30 (9.8)	2 (0.7)
Thorax	30 (9.8)	2 (0.7)
Upper extremity	9 (2.9)	1 (0.3)
Cough	14 (4.6)	0 (0)
Dyspnea	3 (1.0)	0 (0)
Pneumonitis	2 (0.7)	1 (0.3)
Nausea	18 (5.9)	2 (0.7)
Anorexia	12 (3.9)	1 (0.3)
Vomiting	3 (1.0)	0 (0)
Fatigue	71 (23.2)	3 (1.0)
Fever	3 (1.0)	0 (0)

AE, adverse event; HF-WBI, hypofractionated whole breast irradiation.

Table 3 Profiles of seven patients with radiation pneumonitis of grade 2 or higher evaluated by CTCAE v3.0, occurring between 91 days and 3 years from the start of HF-WBI

No. of patient	Grade (CTCAE v3.0)	Time from RT (days)	CLD* of HF-WBI fields (cm)	BI
23	2	288	1.6	−
88	2	215	3.0	−
110	2	533	2.45	+
154	2/2	122/269	2.0	−
184	3/2	166/417	2.4	−
275	2	121	2.6	−
284	2	947	1.69	−

BI, boost irradiation; CLD, central lung distance.

Pneumonitis occurred between 121 and 947 days (mean 324 days, median 269 days).

Two patients (Nos 154, 184) had two events, and one (No. 184) had grade 3 pneumonitis.

HF-WBI was delivered using irradiation fields of the CLD* between 1.6 and 3.0 cm (mean 2.25 cm, median 2.4 cm). One received BI.

Regarding the proportion of treatment completion within the recommended period, 301 patients (96.5%; 95% CI 93.8–98.2%) were treated within the recommended period, including 238 receiving HF-WBI within 29 days (96.7%; 95% CI 93.7–98.6%) and 63 receiving HF-WBI plus BI within 33 days (95.5%; 95% CI 87.3–99.1%).

Evaluation of early AEs found that 38 patients (12.4%) had grade 2, including 25 patients (8.2%) with radiation dermatitis; no patients had grade 3/4 AEs. Table 2 shows the highest scores of early AEs.

For the analysis of the primary endpoint, the proportion of the eight pre-specified late ARs of grade ≥2 occurring between 91 days and 3 years from the start of HF-WBI, 303 (97%) of the 306 patients were included. Three patients were excluded because of a short follow-up period, including one who converted to CF-WBI, one who died from another disease at 1.04 years and one who ended follow-up after 2.02 years. Evaluation of late ARs found 13 patients (4.3%; 95% CI 2.3–7.2) with grade 2/3, including 1 with grade 3 pneumonitis, 6 with grade 2 pneumonitis, 3 with grade 2 breast pain, 2 with grade 2 rib fracture and 1 with grade 2 telangiectasia of the skin. Pneumonitis was the most frequent late AR, and the detailed profiles of patients having pneumonitis are shown in Table 3. None had a grade 4 AR or treatment-related death. Nine of the 238 patients receiving HF-WBI (3.8%; 95% CI 1.7–7.1%) and 4 of the 65 patients receiving HF-WBI plus BI (6.2%; 95% CI 1.7–15.0%) had late ARs of grade 2/3. Finally, the proportion of patients with the eight pre-specified late ARs of grade ≥2 was 4.3% (90% CI 2.6–6.7%), the upper limit of which was under the threshold value of 8% (Table 4), and the safety of HF-WBI was confirmed.

Table 4. Proportion of eight pre-specified late ARs, which included telangiectasia, ulceration, fibrosis, fracture, pneumonitis, cardiac ischemia/infarction, pericardial effusion and pain of grade 2 or higher evaluated by CTCAE v3.0, occurring between 91 days and 3 years from the start of HF-WBI

Patients	Late ARs	% [95%CI] (90%CI)
All receiving HF-WBI	13[b]/303[a]	4.3 [2.3–7.2] (2.6–6.7)
Without BI	9/238	3.8 [1.7–7.1]
With BI	4/65	6.2 [1.7–15.0]

ARs, adverse reactions.

[a]Three patients were excluded: one converted to CF-WBI, one died from another disease at 1.04 years and one ended follow-up in 2.02 years.

[b]13 patients included one with grade 3 pneumonitis, 6 with grade 2 pneumonitis, 3 with grade 2 breast pain, 2 with grade 2 rib fracture and 1 with grade 2 telangiectasia of the skin. No grade 4 or treatment-related deaths occurred.

Discussion

This is the first report of the primary analysis of the safety of short-course HF-WBI after BCS for Japanese women. The present study showed that the proportion of grade 2/3 late ARs of eight pre-specified items, the primary endpoint of this study, was lower than the threshold, along with a favorable outcome for early AEs and acceptable treatment compliance.

As for acute skin toxicities, which are among the most concerning AEs with WBI, the present evaluation of early AEs found 25 patients (8.2%) with grade 2 radiation dermatitis and no patients with grade 3/4. On the other hand, Hickey et al. reviewed randomized, controlled trials of HF-WBI vs CF-WBI in women with early breast cancer after BCS and reported that acute radiation skin toxicity was significantly decreased in HF-WBI, with a risk ratio of 0.32 (95% CI 0.22–0.45) (14). Moreover, the UK FAST-Forward Trial reported that grade 3 acute skin toxicity was observed in 0/43 patients receiving 40 Gy/15 fr/3 weeks, 1/41 (2.1%) receiving 27 Gy/5 fr/1 week and 0/54 receiving 26 Gy/5 fr/1 week (15). Thus, the proportion and grade of acute skin toxicity were small and low in the present and the other trials. One of the reasons for this may be that the biological effective dose (BED) of acute reactions on hypofractionated irradiation may be lower than that of conventional fractionated irradiation. The other reason may be that acute skin toxicity could be affected more by treatment time and total dose of radiation than by the fraction dose.

As for radiation pneumonitis, which is one of the most frequent late ARs with WBI, the present evaluation of late ARs identified seven patients with symptomatic pneumonitis (2.3%), including six with grade 2 and one with grade 3. Two had two episodes during follow-up.

On the other hand, a previous survey had found 9/703 (1.3%) patients with symptomatic pneumonitis, including 6 with grade 2 and 3 with grade 3 (13). Although the proportion of symptomatic pneumonitis in the present trial was slightly higher than that in the previous survey of CF-WBI, the difference was not significant. This small difference might have been caused by the higher detectability of symptomatic pneumonitis in a clinical trial than in a pilot survey of clinical practice. Ishihara et al. found five patients with grade 2 radiation pneumonitis among 327 Japanese patients who underwent HF-WBI and were followed up more than 3 years in a single institution (10). The Ontario Clinical Oncology Group trial (ONTARIO trial) found that there were four cases of radiation pneumonitis (two in HF-WBI arm and two in CF-WBI arm) (5). The UK Standardisation of Breast Cancer Radiotherapy trials (START)-A and -B reported that the incidence of symptomatic lung fibrosis was low during follow-up and was balanced between the treatment schedules (6,7). Radiation pneumonitis seems to be related to the irradiated lung volume and concomitant use of chemotherapy (16,17). Therefore, in the present trial, the CLD in a central axis plane of radiation fields was planned within 3.0 cm, and concurrent chemotherapy was not accepted. All seven patients who had pneumonitis received HF-WBI using irradiation fields with the CLD ≤3.0 cm, and their irradiated lung volume was not larger than that of the others who did not have pneumonitis. Although the optimal dose-volume parameters for ipsilateral lung are not known for HF-WBI, they may be as important as those for CF-WBI, and the irradiated lung volume should be reduced by careful treatment planning to meet CLD ≤3.0 cm.

As for cardiac toxicity, which has been extensively assessed for its potential for excess morbidity associated with the general use of local radiation therapy in breast cancer, no patients had cardiac ischemia/infarction or pericardial effusion in the present evaluation of late ARs between 91 days and 3 years after HF-WBI. However, the follow-up time of 3 years is too short to allow assessment of potential cardiac damage. Darby et al. reported that major coronary events increase linearly with the mean dose delivered to the heart (by 7.4%/Gy), and this increase began within 5 years after exposure and continued for at least 20 years in a population-based case-control study (18). Marhin et al. reported that there was no difference in cardiac mortality between 1140 women receiving CF-WBI with a fraction dose ≤2 Gy and 6307 women receiving HF-WBI with a fraction dose >2 Gy, with a median follow-up of 7.9 years (19). On the other hand, Tjessem et al. explored 20-year cardiac mortality after hypofractionated radiation therapy in breast cancer and reported that the patients receiving a fraction dose of 4.3 Gy had an increased risk of dying of ischemic heart disease compared with both the 2.5 Gy group and the age-matched, cancer-free control group (20). Thus, long-term cardiac ARs caused by high fraction doses have remained uncertain. Therefore, appropriate measures should be taken to exclude the heart from the tangential radiation field of HF-WBI using cardiac-sparing techniques, such as using computer-controlled multi-leaf collimators or intensity-modulated radiation therapy, and dosimetric data about the dose-volume histogram on the coronary artery, the pericardium and the whole heart, as recommended in the American Society for Radiation Oncology (ASTRO) guidelines (21,22).

As for long-term efficacy and cosmetic outcomes, the present follow-up time was too short to evaluate them in early-stage breast cancer patients who will have a long life after treatment. Referring to Western randomized trials, for example, ONTARIO trial reported that the 10-year local control rate and cosmetic outcome with HF-WBI was not inferior to that with CF-WBI (5,8). For the other examples, UKSTART trials reported that 10-year rates of local–regional relapse did not differ significantly between HF-WBI and CF-WBI (6,7,9). However, it should be noted that ONTARIO trial excluded women with pathologically positive lymph nodes or surgical margins, while the present trial included 37 patients (12%) with pathologically N1a and 66 patients (21.5%) with pathologically close surgical margins. In addition, it should be noted that the START trials included patients receiving post-mastectomy irradiation and CF-BI of 10 Gy/5 fr/5 days, while the present trial included no patients after mastectomy and 66 patients (21.5%) receiving HF-BI of 10.64 Gy/4 fr/4 days. Moreover, all of the Western randomized trials included no or few Japanese women. For these reasons, their results are not directly applicable to Japanese clinical practice of WBI after BCS. Therefore, further follow-up is important to analyze long-term efficacy and cosmetic outcomes in our original patients.

An appropriate method of HF-WBI has not yet been established, because the radiation treatment factors, such as fraction doses, total doses, treatment time, with/without BI, with/without regional nodal irradiation, and so on were very different between trials. Our group used the HF-WBI schemes (42.56 Gy in 16 fractions over 22 days) which were the same as those of the ONTARIO trial (5,8). Their trial was the first randomized trial to compare HF-WBI with CF-WBI and had the longest follow-up time, and their HF-WBI schedule was favored by the task force that published the ASTRO guideline 2011 on HF-WBI (21). After that, the ASTRO guideline 2018 (22) recommended that the preferred dose-fractionation scheme for women with invasive breast cancer receiving WBI with or without inclusion of the low axilla is HF-WBI to a dose of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions, showing a strong recommendation strength, a high quality of evidence and 100% of consensus. As for a tumor bed boost, ONTARIO trial included no patient receiving a boost, and the optimal boost dose is not known. Therefore, a tumor bed boost of 10.64 Gy in four fractions over 4 days using a fraction dose of 2.66 Gy, which was the same as that of HF-WBI, was used when the surgical margin was ≤5 mm, so that the BED of HF-WBI plus BI would correspond to that of CF-WBI plus BI. The ASTRO guideline 2018 (22) recommended that 10 Gy in four to five fractions was suggested as the standard tumor bed boost dose-fraction, regardless of whole breast dose-fractionation, showing a conditional recommendation strength, a moderate quality of evidence and 100% of consensus.

In conclusion, this first report of the primary analysis showed the safety within 3 years after HF-WBI for Japanese women with margin-negative invasive breast cancer after BCS and suggested that HF-WBI is one of the standard treatments and applicable to Japanese clinical practice in early-stage breast cancer. Longer follow-up will have to be continued to evaluate long-term survival and cosmetic changes, related to uncertain and unexpected late ARs of normal tissues caused by high-fraction dose irradiation.

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Conflict of interest statement

All authors have no commercial or financial involvement in connection with this study and declare that no conflict of interest.

Appendix

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