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Original Article

Significance of Hypofractionated Radiotherapy in Postoperative Irradiation for Breast Cancer: An Asian Multi-institutional Prospective Study

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Abstract

Aims: There is a need for the adequate distribution of healthcare resources in Southeast Asia. Many countries in the region have more patients with advanced breast cancer who are eligible for postmastectomy radiotherapy (PMRT). Therefore, it is critical that hypofractionated PMRT is effective in most of these patients. This study investigated the significance of postoperative hypofractionated radiotherapy in patients with breast cancer, including advanced breast cancer, in these countries.

Materials and methods: Eighteen facilities in 10 Asian countries participated in this prospective, interventional, single-arm study. The study included two independent regimens: hypofractionated whole-breast irradiation (WBI) for patients who had undergone breast-conserving surgery and hypofractionated PMRT for patients who had undergone total mastectomy at a dose of 43.2 Gy in 16 fractions. In the hypofractionated WBI group, patients with high-grade factors received additional 8.1 Gy boost irradiation sessions for the tumour bed in three fractions.

Results: Between February 2013 and October 2019, 227 and 222 patients were enrolled in the hypofractionated WBI and hypofractionated PMRT groups, respectively. The median follow-up periods in the hypofractionated WBI and hypofractionated PMRT groups were 61 and 60 months, respectively. The 5-year locoregional control rates were 98.9% (95% confidence interval 97.4–100.0) and 96.3% (95% confidence interval 93.2–99.4) in the hypofractionated WBI and hypofractionated PMRT groups, respectively. Regarding adverse events, grade 3 acute dermatitis was observed in 2.2% and 4.9% of patients in the hypofractionated WBI and hypofractionated PMRT groups, respectively. However, no other adverse events were observed.

Conclusion: Although further follow-up is required, hypofractionated radiotherapy regimens for postoperative patients with breast cancer in East and Southeast Asian countries are effective and safe. In particular, the proven efficacy of hypofractionated PMRT indicates that more patients with advanced breast cancer can receive appropriate care in these countries. Hypofractionated WBI and hypofractionated PMRT are reasonable approaches that can contain cancer care costs in these countries. Long-term observation is required to validate our findings.

Key words: Adjuvant radiotherapy; breast neoplasm; breast-conserving surgery; clinical trial; hypofractionation; mastectomy

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Introduction

Breast cancer is a common cancer worldwide. In 2020, female breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases worldwide [1]. In particular, the incidence rates of breast cancer are rising rapidly in developing countries in South America, Africa and Asia [1]. Radiotherapy, together with surgery and systemic therapies, plays a crucial role in the treatment of breast cancer. Its specific function is to prevent local and regional lymph node recurrences. Regardless of age, tumour characteristics, or systemic therapy, the effect of radiotherapy on local control is seen at a constant rate, with a greater efficacy in patients who have a higher risk of local recurrence [2]. Moreover, radiotherapy improves the survival rate after breast-conserving surgery (BCS), regardless of axillary lymph node metastasis [2]. Thus, unless the patient is pregnant or has a specific genetic disorder, radiotherapy is highly recommended [3,4].

Evidence is accumulating for whole-breast irradiation (WBI) after BCS to support the clinical benefit of hypofractionated WBI. A Canadian randomised controlled trial (RCT) compared 42.5 Gy hypofractionated WBI in 16 fractions to 50 Gy in 25 fractions and found no differences in the 10-year local recurrence rates, overall survival or tolerability [5]. Age, tumour size, oestrogen receptor expression and systemic therapy did not affect local recurrence rates [6]. Studies on the hypofractionated WBI regimen, such as the START-A and START-B trials reported from the UK, have been conducted to determine the optimal dose of hypofractionated WBI [7]. The frequency of side-effects, such as breast atrophy, telangiectasia and breast oedema, was lower when using hypofractionated WBI in the START-A and START-B trials, compared with that with conventional fractionations [7]. The latest American Society for Radiation Oncology guideline consensus recommends hypofractionated WBI at a dose of 40–42.5 Gy in 15–16 fractions for breast cancer patients after BCS [8]. Postmastectomy radiotherapy (PMRT) is recommended for patients with locally advanced breast cancer to reduce local and regional lymph node recurrence and improve survival in patients undergoing total mastectomy with four or more axillary nodes [9,10]. The significance of hypofractionated PMRT was reported over 20 years ago [11]. Recently, attempts to validate the use of hypofractionated PMRT have been expanding [12–15]. Long-term outcomes based on prospective RCTs that directly compare the efficacy of hypofractionated PMRT to standard fractionated radiotherapy have not yet been reported. However, considering medical costs and patient convenience, hypofractionated PMRT is as attractive a treatment option as hypofractionated WBI.

Although a high level of evidence on hypofractionated WBI and hypofractionated PMRT has been gathered, there is insufficient verification that the evidence is clinically feasible and reliable in low- and middle-income Asian countries, where the number of breast cancer patients is increasing and healthcare resources are limited (see Supplementary Table S1). In Southeast Asia, there is a strong need to adequately distribute limited healthcare resources [1]. Patients with breast cancer in developing Asian countries present at a younger age, at later stages, and are more likely to die from the disease than those in Western countries [16]. Due to limited resources, radiation oncologists can only treat a limited number of patients. Thus, establishing an efficient radiotherapy method over a short period is an urgent issue for the treatment of more patients.

Notably, a recent study indicated racial/ethnic differences in response to radiotherapy in breast cancer patients [17]. The nomogram from Memorial Sloan Kettering Cancer Centre uses up to 10 variables, including radiotherapy, for the prediction of ipsilateral breast tumour recurrence [18], whereas Wang *et al.* [17] validated the nomogram in an Asian population and found that just three factors (age, adjuvant endocrine therapy and comedo-necrosis) could predict the local recurrence. The fact that radiotherapy did not contribute as a significant predictor of local recurrence in this validation in Asians suggests that the contribution of radiotherapy to local control may vary by race. Thus, there is a need to establish a high level of clinical evidence of radiotherapy in Asian populations while considering racial differences.

The Forum for Nuclear Cooperation in Asia (FNCA) is a framework for regional cooperation among Asian countries under the leadership of Japan to apply nuclear science and technology securely and peacefully. The Radiation Oncology Project of FNCA was established in 1993 to address this issue in the field of radiotherapy. The goal of this project was to standardise radiotherapy and improve the clinical outcomes of common cancers in Asia [19,20]. Hence, we report the significance of hypofractionated radiotherapy in postoperative breast cancer patients in East and Southeast Asian countries within the framework of FNCA.

Materials and Methods

Study Design

This was a prospective, interventional, single-arm study that used the FNCA Radiation Oncology Project framework, which includes, at present, 11 countries: the People's Republic of Bangladesh, the People's Republic of China, the Republic of Indonesia, Japan, the Republic of Kazakhstan, the Republic of Korea, Malaysia, Mongolia, the Republic of the Philippines, the Kingdom of Thailand and the Socialist Republic of Vietnam. Eighteen facilities in 10 countries participated in this study (with the exception of Malaysia). The participating institutions have been listed in Supplementary Table S2. This study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board of each participating centre and enrolled in the University Medical Information Network Clinical Trials Registry (ID: 000010977). Written informed consent was obtained from all patients. This study included hypofractionated WBI

for post-BCS patients and hypofractionated PMRT for postmastectomy patients. The inclusion and exclusion criteria are presented in Table 1.

Treatment Regimens

Radiotherapy was performed in the supine position, with the upper limbs raised. Regional radiotherapy using X-rays or cobalt-60 was delivered using two opposing tangential fields, with the treatment provided daily from Monday to Friday. In facilities where intensity-modulated radiotherapy was available, irradiation using intensity-modulated radiotherapy was permitted.

WBI at a dose of 43.2 Gy in 16 fractions was applied to the hypofractionated WBI group. Patients with high-grade factors, including age <50 years, axillary lymph node metastasis, lymphovascular invasion and positive or close margins, were administered an additional 8.1 Gy in three fractions of boost irradiation to the tumour bed in the hypofractionated WBI group. Boost irradiation of the tumour bed was carried out in a single anterior field with electron beams or cobalt-60 once daily for 3 consecutive days.

Chest wall and supraclavicular fossa irradiation at a dose of 43.2 Gy in 16 fractions was applied to the hypofractionated PMRT group. Boost irradiation was not provided regardless of surgical technique or N staging in the hypofractionated PMRT group.

The breast tissue or targeted chest wall dose was restricted to <107% of the prescribed dose. Doses to the heart, contralateral breast, lungs and other normal tissues were minimised according to the criteria of each facility. Systemic therapy, including neoadjuvant or adjuvant therapy, was administered according to the National Comprehensive Cancer Network guidelines [21]. Concurrent chemo- and/or endocrine therapies were not permitted.

Endpoints

The primary endpoint was the locoregional control (LRC) rate. The secondary endpoints were the disease-free survival (DFS) rate, overall survival rate and the incidence of acute and late adverse events in the hypofractionated WBI and hypofractionated PMRT groups. Cosmetic outcomes were recorded as secondary endpoints in the hypofractionated WBI group. The start date of each observation period was the date of the start of radiotherapy. Physicians at each institution independently adjudicated the recurrence, cause of death and adverse events with supporting documentation. Acute adverse events (observed 90 days after the initiation of radiotherapy) were assessed with CTCAE v4.0 [22]. Late adverse events (observed after 91 days) were assessed by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (EORTC) [23]. For the evaluation of adverse events, the highest score within the observation period was recorded. The EORTC cosmetic rating system was used for the evaluation of the cosmetic outcomes in the hypofractionated WBI group [24]. This evaluation method uses a four-point scale from 'excellent' to 'poor' and the worst deteriorated condition during the treatment period was recorded. All data were approved by the physicians at the annual FNCA meeting.

Follow-up Schedule

After the completion of radiation therapy, patients were followed up every 6 months for 5 years and then annually. At each visit, a history was obtained, and a physical examination was carried out. If a patient was unable to attend a scheduled follow-up visit, the physician called the patient or the patient's family. Late adverse events and cosmetic outcomes were assessed at the same time points.

Table 1
Inclusion and exclusion criteria

Inclusion criteria	
Hypofractionated whole-breast irradiation	Hypofractionated postmastectomy radiotherapy
Patients who have undergone breast-conserving surgery	Patients who have undergone mastectomy
Histopathologically confirmed breast cancer	Histopathologically confirmed breast cancer
T stage is either Tis, T1 or T2	Patients without positive margin
Undergone a lymph node dissection or sentinel lymph node biopsy	Undergone a lymph node dissection
Fewer than three positive axillary lymph nodes	Fewer than eight positive lymph nodes
Written informed consent obtained	Written informed consent obtained
Exclusion criteria (common)	
Patients with parasternal lymph node metastasis	
Patients with residual axillary lymph nodes or axillary irradiation	
Patients with distant metastasis	
Patients with collagen disease	
Patients with active multiple cancers (epithelial cancer and bilateral breast cancer are acceptable)	
Patients receiving concurrent chemotherapy	
Patients with a history of radiation therapy to the chest	
Patients who are pregnant or may become pregnant	

Statistical Analysis

The rate of LRC at 5 years in both the hypofractionated WBI and hypofractionated PMRT groups was assumed to be 95% (a threshold LRC of 92% and expected LRC of 97%). The sample size was estimated to be 191 patients per group based on assumptions, with a power of 90% (two-sided alpha level of 5%). Considering the number of patients lost to follow-up, we enrolled 200 patients in both groups. LRC was defined as the time after radiotherapy that the patient survived without recurrence within the irradiated field. DFS was defined as the time after radiotherapy for which the patient survived without any breast cancer recurrence. Overall survival was defined as the time to death from any cause. These periods were estimated using the Kaplan–Meier method. The univariate analyses used the Log-rank test. All factors that showed statistically significant associations in univariate analyses were included in multivariate analyses with Cox proportional hazards regression models. The level of statistical significance was set at $P < 0.05$, and all statistical tests were two-sided. IBM SPSS Statistics 27 was used to perform statistical calculations (IBM, Armonk, NY, USA).

Results

Between February 2013 and October 2019, 227 and 222 patients were enrolled in the hypofractionated WBI and hypofractionated PMRT groups, respectively. All the patients satisfied the eligibility criteria. The median follow-up periods were 61 and 60 months in the hypofractionated WBI and hypofractionated PMRT groups, respectively. Table 2 shows the patient, tumour and treatment characteristics of both groups. The hypofractionated WBI group included one patient with bilateral breast cancer. Thus, 228 irradiated breasts in 227 cases were evaluated. The hypofractionated WBI group included 37 patients with ductal carcinoma *in situ* (DCIS); however, none of the cases were stage T3–4. The hypofractionated PMRT group did not include patients with DCIS; however, it did include 38 patients with T3–4 stage. Boost irradiation of the tumour bed was provided to 74.1% of patients in the hypofractionated WBI group. Fifty-seven patients had non-luminal type tumours; 40 (70.2%) of them received boost irradiation.

Oncological Outcomes

Two and six patients in the hypofractionated WBI and hypofractionated PMRT groups, respectively, had locoregional recurrence at the latest follow-up. In the hypofractionated WBI group, 12 patients had died by the latest follow-up: four of them died due to breast cancer recurrence; the remaining eight died due to other reasons (five other cancer deaths and three non-cancer deaths). In the hypofractionated PMRT group, 20 patients had died by the latest follow-up: 15 of them died due to breast cancer recurrence; the remaining five died due to other reasons (one other cancer death and four non-cancer deaths).

Figure 1 shows the clinical outcomes of this study. In the hypofractionated WBI group, the 5-year LRC, overall survival and DFS rates were 98.9% (95% confidence interval 97.4–100.0), 95.9% (95% confidence interval 93.0–98.7) and 95.5% (95% confidence interval 92.6–98.4), respectively. In the hypofractionated PMRT group, the 5-year LRC, overall survival and DFS rates were 96.3% (95% confidence interval 93.2–99.4), 90.9% (95% confidence interval 86.5–95.3) and 81.0% (95% confidence interval 74.3–87.8), respectively. In the univariate analysis for the hypofractionated WBI group, none of the factors analysed, including molecular subtype, were found to be associated with LRC; however, the N stage was associated with overall survival ($P = 0.016$) and DFS ($P = 0.002$) (Table 3). Similar trends were seen in the hypofractionated PMRT group; none of the factors were associated with LRC, but the N stage was associated with overall survival ($P = 0.007$) and DFS ($P = 0.012$) (Table 4).

Adverse Events and Cosmetic Outcomes

Regarding acute adverse events, grade 3 dermatitis was observed in 2.2% and 4.9% of patients in the hypofractionated WBI and hypofractionated PMRT groups, respectively. However, no grade 3 acute adverse events, other than dermatitis, were observed (Table 5). Regarding late adverse events, a few patients had grade 2 skin, subcutaneous tissue and lung damage. However, no late adverse events above grade 3 were observed (Table 5). Cosmetic outcomes remained 'excellent' in 64.5% of patients and were classified as 'fair' and 'poor' in 1.3% of patients each (see Supplementary Table S3).

Discussion

This study aimed to determine whether hypofractionated irradiation could be effective and safe in patients with postoperative breast cancer in East and Southeast Asia. Excellent LRC rates were achieved in the hypofractionated WBI and hypofractionated PMRT groups, and the incidence of adverse events was acceptable. This study showed the significance and efficacy of hypofractionation for postoperative breast cancer patients based on data from a multinational, multicentre, Asian study.

In the hypofractionated WBI group, the 5-year LRC rate was 98.9%, indicating an excellent therapeutic outcome. In addition, the incidence of adverse events in the hypofractionated WBI group was very low, with no late adverse events $\geq$ grade 3. Excellent results were also observed in the DCIS patients. All patients with DCIS were recurrence-free at 5 years (Table 3). Previous RCTs did not include patients with DCIS [5–7]. Randomised results on hypofractionated WBI in patients who underwent BCS for DCIS were missing. The Danish Breast Cancer Group conducted a phase III RCT for patients with DCIS [25]. Their study revealed that 40 Gy hypofractionated WBI in 15 fractions for DCIS did not result

Table 2
Patients, tumour and treatment characteristics

Characteristics	Hypofractionated WBI	Hypofractionated PMRT
No. cases/breasts	227/228	222/222
Age, median (range) years	49 (24–79)	49 (24–80)
Country: BGD/CHN/IDN/JPN/KAZ/KOR/MGL/PHL/THA/VNM	31/6/16/134/14/9/3/0/14/0	84/13/0/15/20/0/26/18/0/46
Age, <50 years (%)	50.2%	50.9%
Premenopause/menopause	121/106	104/118
Tumour site, right/left	116/112	108/114
T stage: is/1/2/3/4	37/136/55/0/0	0/31/153/31/7
N stage: 0/1/2/3	196/32/0/0	58/117/44/3
Clinical stage: 0/I/II/III/IV	36/124/68/0/0	0/0/156/65/1
Histological subtype: DCIS/IDC/others	37/168/23	0/206/16
Molecular subtype: luminal/HER2E/basal/others	171/11/29/17	159/26/34/3
Neoadjuvant chemotherapy, yes (%)	2.2%	28.8%
Adjuvant chemotherapy, yes (%)	30.8%	76.1%
Endocrine therapy, yes (%)	62.1%	38.7%
Main radiotherapy method: cobalt-60/X-ray/IMRT	15/210/3	40/180/2
Boost irradiation, yes (%)	74.1%	N/A
Radiotherapy period, median (range) days	26 (18–50)	21 (16–45)

BGD, People's Republic of Bangladesh; CHN, People's Republic of China; DCIS, ductal carcinoma *in situ*; HER2E, human epidermal growth factor receptor 2-enriched; IDC, invasive ductal carcinoma; IDN, Republic of Indonesia; IMRT, intensity-modulated radiotherapy; is, *in situ*; JPN, Japan; KAZ, Republic of Kazakhstan; KOR, Republic of Korea; MGL, Mongolia; N, lymph node; PHL, Republic of the Philippines; PMRT, postmastectomy radiotherapy; T, tumour; THA, Kingdom of Thailand; VNM, Socialist Republic of Vietnam; WBI, whole-breast irradiation.

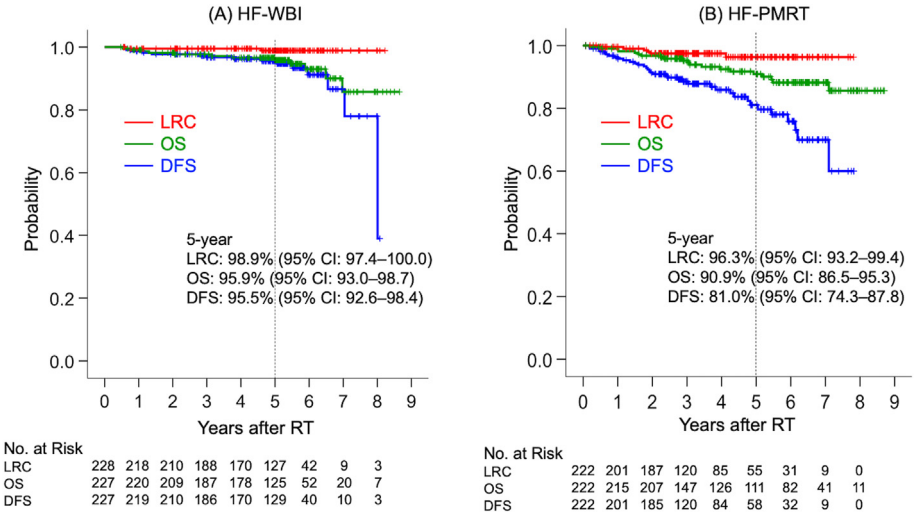

Fig 1. Kaplan–Meier curves for oncological outcomes: (A) the hypofractionated whole-breast irradiation (HF-WBI) group; the hypofractionated postmastectomy radiotherapy (HF-PMRT) group. The red lines indicate locoregional control (LRC) rates, the green lines indicate overall survival (OS) rates and the blue lines indicate disease-free survival (DFS) rates. RT, radiotherapy.

in more breast induration than standard fractionated radiotherapy at 50 Gy in 25 fractions. Other adverse events were minimal. The results of our study reinforce the validity of hypofractionated WBI after BCS for early breast cancer, including DCIS, in the Asian population.

Molecular subtypes did not affect LRC in our study and showed excellent LRC regardless of the molecular subtype. Molecular subtype could affect LRC following BCS and WBI [6,26,27]. The small sample size may be the reason why the molecular subtype did not affect LRC in our study. As another possible reason, the absence or presence of boost irradiation may explain this discrepancy. An RCT in which Bane *et al.* [5,6] analysed the biological characteristics, including these molecular subtypes, did not apply boost irradiation. Recently, Fodor *et al.* [28] reported that the molecular subtype had an impact in 1325 early breast cancer patients treated with hypofractionated WBI without boost irradiation and showed that a tumour's molecular subtype affects LRC if boost irradiation is not applied. In our study, the molecular subtype was not considered as an indication for boost irradiation; however, most (70.1%) non-luminal-type patients received boost irradiation. The importance of boost irradiation in hypofractionated WBI should be noted. An RCT comparing the results of

Table 3
Assessment of prognostic factors in hypofractionated whole-breast irradiation with univariate analysis

Factors	Number of patients	LRC		Overall survival		DFS	
		5-year (%)	*P* value	5-year (%)	*P* value	5-year (%)	*P* value
Age (years)			0.180		0.635		0.316
<50	115*	98.0		94.9		91.9	
≥50	112	100.0		96.8		96.8	
T stage			0.414		0.724		0.867
Tis–T1	171	98.6		95.1		94.5	
T2	56*	100.0		98.2		93.5	
N stage			0.121		0.016		0.002
N0	196	99.3		97.7		97.0	
N1	31*	96.8		84.8		76.1	
Histological subtype			0.485		0.148		0.088
DCIS	37	100.0		100.0		100.0	
IDC	167*	98.5		94.3		91.9	
Others	23	100.0		100.0		100.0	
Molecular subtype			0.375		0.184		0.350
Luminal	170	99.2		98.1		95.7	
HER2E/basal/others	57*	98.2		89.0		89.3	
Boost irradiation			0.408		0.197		0.487
No	59	100.0		96.2		93.3	
Yes	168*	98.5		95.7		94.5	

DCIS, ductal carcinoma *in situ*; DFS, disease-free survival; HER2E, human epidermal growth factor receptor 2-enriched; IDC, invasive ductal carcinoma; is, *in situ*; LRC, locoregional control; N, lymph node; T, tumour.

* One patient with bilateral breast cancer was placed in the group according to patient or tumour characteristics. The patient was 46 years old; T1N1 (IDC, luminal), T2N1 (IDC, triple-negative) and boost irradiation.

radiotherapy with or without boost irradiation for the molecular subtypes of breast cancer is warranted.

Following hypofractionated WBI after BCS for early-stage breast cancer, evidence on hypofractionated PMRT after total mastectomy for advanced breast cancer has been accumulating [11–15]. A prospective RCT has recently been reported [29]. The local efficacy in these studies was reported as a 5-year LRC rate of 86.6–96.0% or 7-year LRC rate of 93.0%. The 5-year LRC rate in the current study was 96.3%, which indicated good LRC regardless of the prognostic factors. Thus, our data support the feasibility of hypofractionated PMRT based on data from a prospective multicentre trial in Asia. The use of hypofractionated PMRT would further expand in future.

The incidence of adverse events was low in both the acute and late phases. No late adverse events greater than

Table 4
Assessment of prognostic factors in hypofractionated postmastectomy radiotherapy with univariate analysis

Factors	Number of patients	LRC		Overall survival		DFS	
		5-year (%)	*P* value	5-year (%)	*P* value	5-year (%)	*P* value
Age (years)			0.946		0.127		0.317
<50	113	95.7		92.9		86.1	
≥50	109	96.8		88.8		71.3	
T stage			0.902		0.328		0.783
T1–2	184	96.0		90.7		78.2	
T3–4	38	97.3		91.9		78.7	
N stage			0.494		0.007		0.012
N0–1	175	96.6		93.6		80.1	
N2–3	47	95.3		79.9		71.2	
Histological subtype			0.487		0.681		0.973
IDC	206	96.0		90.9		77.4	
Others	16	100.0		90.9		80.0	
Molecular subtype			0.140		0.775		0.626
Luminal	159	95.1		91.2		78.3	
HER2E/basal/others	63	100.0		89.5		75.9	

DFS, disease-free survival; HER2E, human epidermal growth factor receptor 2-enriched; IDC, invasive ductal carcinoma; LRC, locoregional control; N, lymph node; T, tumour.

Table 5
List of the highest scores of acute and late adverse events

	Hypofractionated whole-breast irradiation ($n = 227$)				Hypofractionated postmastectomy radiotherapy ($n = 222$)			
Acute adverse events	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
Skin	17 (7.5%)	181 (79.7%)	24 (10.6%)	5 (2.2%)	50 (22.5%)	138 (62.2%)	23 (10.4%)	11 (4.9%)
Breast/subcutaneous	199 (87.7%)	28 (12.3%)	0 (0.0%)	0 (0.0%)	175 (78.8%)	45 (20.3%)	2 (0.9%)	0 (0.0%)
Lung	225 (99.1%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	208 (93.7%)	14 (6.3%)	0 (0.0%)	0 (0.0%)
Late adverse events	Grade 0	Grade 1	Grade 2	Grade 3+	Grade 0	Grade 1	Grade 2	Grade 3+
Skin	177 (78.0%)	48 (21.1%)	2 (0.9%)	0 (0.0%)	127 (57.2%)	93 (41.9%)	2 (0.9%)	0 (0.0%)
Breast/subcutaneous	195 (85.9%)	31 (13.7%)	1 (0.4%)	0 (0.0%)	176 (79.3%)	42 (18.9%)	4 (1.8%)	0 (0.0%)
Lung	222 (97.8%)	4 (1.8%)	1 (0.4%)	0 (0.0%)	208 (93.7%)	13 (5.9%)	1 (0.4%)	0 (0.0%)
Heart	227 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	218 (98.2%)	4 (1.8%)	0 (0.0%)	0 (0.0%)
Rib fracture	227 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	222 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

grade 3 were observed. A previous study reported that grade 3 late skin toxicity and subcutaneous tissue toxicity were evident in 2.5% and 2.5% of patients 10 years after treatment with hypofractionated WBI [5]. Studies performing long-term toxicity evaluations after hypofractionated PMRT are still limited; however, Chitapanarux *et al.* [14] reported that grade 3 or higher skin toxicity was seen in about 2% of patients. Grade 3 late skin and subcutaneous tissue toxicity may be evident ≥5 years after radiotherapy. In addition, lung and cardiac toxicity are important late adverse events associated with postoperative irradiation for breast cancer [30,31]. This study did not examine the relationship between dose and adverse events in these organs at risk because of the lower incidence of these events. Long-term follow-up is necessary for cardiotoxicity, considering the effects of radiation dose and aging [31]. Therefore, a long-term re-evaluation of adverse events is warranted.

There are several limitations to this study. First, the median follow-up after radiotherapy was short (about 5 years in both groups). Therefore, re-evaluation of these findings after prolonged observation is required. Second, this study did not compare the hypofractionated regimen to the 1.8–2.0 Gy per fraction regimen. Given the increase in breast cancer patients at the hospitals in this study and the imbalance of limited radiotherapy recourses, it may be challenging to conduct a comparative trial with a regimen that includes conventional fractionation (1.8–2.0 Gy per fraction). Third, the impact of breast cancer surgery and systemic therapy on treatment outcomes was not discussed because this was not a comparative study, and the clinical outcomes were satisfactory. However, a comprehensive analysis may be necessary for future re-evaluation after long-term follow-up.

In conclusion, it was strongly suggested that hypofractionated radiotherapy regimens for postoperative breast cancer patients in East and Southeast Asian countries are effective and safe. In particular, the proven efficacy of hypofractionated PMRT means more patients with advanced breast cancer can receive appropriate care in these countries. Hypofractionated WBI and hypofractionated PMRT are reasonable approaches that can contain cancer care costs in these countries. Long-term observation is required to validate our findings.

Author Contributions

NO, SaK, KK and ShK are the guarantors of integrity of the entire study. KK was responsible for study concepts and design. NO, SaK, KK, PAB, XX, DE, TA, WIJ, EY, MJC, KT, TAD, WNPN and ShK were responsible for the clinical studies. NO and SaK were responsible for experimental studies/data analysis. NO was responsible for the statistical analysis. NO and KK prepared the manuscript. KK, KT and ShK edited the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2023.04.007.

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