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Hypofractionated volumetric-modulated arc therapy for breast cancer: A propensity-score-weighted comparison of radiation-related toxicity

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Abstract

We assessed the clinical benefit of combining volumetric-modulated arc therapy (VMAT) and hypofractionated radiotherapy (HF-RT) considering the incidence of radiation-related toxicities. After a retrospective review for breast cancer patients treated with adjuvant RT between 2005 and 2017, a total of 4209 patients treated with three-dimensional conventional fractionation (CF-3D, 50.4 Gy/28 fractions) and 1540 patients treated with HF-RT (768 received HF-3D; 772, HF-VMAT; 40 Gy/15 fractions) were included. A total of 2229 patients (38.8%) received regional node irradiation (RNI): 1642 (39.0%), 167 (21.7%) and 420 (54.4%) received RNI via CF-3D, HF-3D and HF-VMAT, respectively. Acute/subacute and late toxicities were evaluated. Propensity scores were calculated via logistic regression. Grade 2+ acute/subacute toxicities was the highest in CF-3D group (15.0%, 2.6% and 1.6% in CF-3D, HF-3D and HF-VMAT, respectively; $P < .001$). HF-VMAT reduced Grade 2+ acute/subacute toxicities significantly compared to CF-3D (odds ratio [OR] 0.11, $P < .001$) and HF-3D (OR 0.45, $P = .010$). The 3-year cumulative rate of late toxicities was 18.0% (20.1%, 10.9% and 13.4% in CF-3D, HF-3D and HF-VMAT, respectively; $P < .001$). On sensitivity analysis, the benefit of HF-VMAT was high in the RNI group. Acute and late toxicities were fewer after HF-VMAT than after HF-3D or CF-3D, especially in women who underwent RNI.

KEYWORDS
breast cancer, hypofractionated radiotherapy, radiotherapy dose fractionation, toxicity, volumetric-modulated arc therapy

1 | INTRODUCTION

Hypofractionated radiotherapy (HF-RT) and standard conventional fractionation (CF) are equally safe and effective,[1-4] with the 3-week schedule of 42.5 Gy in 16 fractions or 40 Gy in 15 fractions[3,5] being the most popular HF regimen.[6,7] Most HF regimens result in comparable local control and less frequent toxic events with a lower biologically effective dose (40 Gy in 15 fractions or 39 Gy in 13 fractions).[3,5] Although the use of HF-RT for whole breast irradiation is gradually increasing,[6] some physicians avoid using it owing to possible RT-related toxicities because of large fraction sizes.[8]

Although several dosimetric studies have compared three-dimensional (3D) conformal RT and intensity-modulated RT (IMRT) for breast cancer, only a few clinical studies have investigated IMRT.

Abbreviations: 3D, three-dimensional; CF, conventional fractionation; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; HF-RT, hypofractionated radiotherapy; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; IPTW, inverse probability of treatment-weighted; IQR, interquartile range; OR, odds ratio; RNI, regional node irradiation; RTOG, Radiation Therapy Oncology Group; VMAT, volumetric-modulated arc therapy.

Highly conformal techniques are the best to optimize the convenience of HF-RT while reducing the toxicity, although limited data are available proving the superiority of the combination of HF-RT and volumetric-modulated arc therapy (VMAT), an IMRT technique.

Therefore, we aimed to determine the clinical benefit of IMRT with hypofractionation (40 Gy in 15 fractions) by comparing patients treated with CF-3D, HF-3D and HF-VMAT, considering the incidence of radiation-related toxicities and locoregional recurrence.

What's new?

Hypofractionated radiotherapy (HF-RT) is increasingly used for whole breast irradiation. However, concerns of possible radiation-related toxicities persist. Here, in a cohort of breast cancer patients treated with adjuvant RT, the clinical benefits of intensity-modulated RT (IMRT) with HF were compared with three-dimensional conventional fractionation (CF-3D), HF-3D, and HF volumetric-modulated arc therapy (HF-VMAT). Compared to CF-3D and HF-3D, a three-week schedule of 40 Gy in 15 fractions of HF-VMAT had the lowest rate of radiation-related acute and late toxicities. HF-VMAT also had fewer subacute toxicities. The findings indicate that HF-VMAT can significantly benefit breast cancer patients treated with regional node irradiation.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients with newly diagnosed breast cancer, who underwent curative surgery between January 2005 and December 2017 at Yonsei Cancer Center, were included. Exclusion criteria were: (a) diagnosis of adenoid cystic carcinoma/angiosarcoma; (b) follow-up duration <1 year; and (c) incomplete course of RT. We identified and included 5749 patients: 4209 received CF-RT using 3D-RT (the CF-3D group), 768 received HF-RT using 3D-RT (the HF-3D group) and 772 received HF-RT using VMAT (the HF-VMAT group). No patient received CF-VMAT. This study was approved by the institutional review board (No. 4-2020-0131); the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was conducted in accordance with the STROBE guidelines.

2.2 | Radiotherapy

All patients underwent simulation computed tomography (CT) for RT planning. Techniques for immobilization differed based on the institutional protocol.[9]

As per the Korean national insurance program, VMAT is only allowed for patients treated with HF regimens (to improve dose homogeneity). Two tangential photons with the wedge or field-in-field technique (CF-3D or HF-3D) or VMAT using two partial arcs (HF-VMAT) were utilized in all patients who underwent breast-conserving surgery. Patients who underwent mastectomy received chest wall (or reconstructed breast) RT with regional node irradiation (RNI) using the reverse-hockey stick technique (CF-3D), partial wide tangential technique (HF-3D) or VMAT using two partial arcs (HF-VMAT).[10] Since 2008, comprehensive RNI routinely includes internal mammary, axillary and supraclavicular lymph nodal chains in patients with N2+ disease or high-risk N0 disease (tumors >2 cm and high-grade or basal type).[11] Among 2308 patients who received RNI, the internal mammary node was irradiated in 2229 patients (96.6%). Internal mammary irradiation was adopted using the partial wide tangential field or reverse-hockey stick technique in the CF-3D group, a partial wide tangential field in the HF-3D group and two partial arcs in the HF-VMAT group.[12-14] In patients who underwent breast-conserving surgery, an extended tangential field to cover the intercostal space of the first three ribs blocking the lower internal mammary node to spare the lung and heart.[13] A reverse-hockey stick technique, adopted in patients after mastectomy, consisted of an electron field covering 80% of prescription dose to the chest wall and internal mammary node chain with individualized custom bolus and photon field treating lateral chest wall, axillary and supraclavicular lymph node area.[14] Since the adoption of HF-RT in our institution, the extent of axillary lymph nodes during RNI has reduced from axillary levels I-III to II (partial)-III, especially when full-node dissection was performed. In total, 2229 patients (38.8%) received RNI: 1642 (39.0%), 167 (21.7%) and 420 (54.4%) patients in the CF-3D, HF-3D and HF-VMAT groups, respectively. In the CF-3D group, 1468 patients received RNI covering axillary lymph node levels I-III (89.4% of patients who received RNI), whereas 163 (97.6% of patients who received RNI) and 324 patients in the HF-3D and HF-VMAT groups, respectively (77.1% of patients who received RNI), received RNI covering axillary lymph node levels II (partial)-III. Multiple cardiac-sparing RT techniques (including deep-inspiration breath-holding, prone positioning, continuous positive airway pressure and VMAT) were implemented; 653 (11.4%) and 13 (0.2%) patients were treated using deep-inspiration breath-holding and prone positioning, respectively.

Target volumes were earlier contoured using the Radiation Therapy Oncology Group (RTOG) guidelines, but since 2015, they were contoured using the European Society for Radiotherapy and Oncology guidelines, following their validation.[15] A dose of 50.4 Gy in 28 fractions was prescribed to the CF-3D group and 40.05 Gy in 15 fractions was prescribed to the HF-3D and HF-VMAT groups. Dose constraints for organs-at-risk in the CF-3D group were based on the Danish Breast Cancer Cooperative Group guideline.[16] Regarding internal mammary irradiation, mean heart dose constraints of $\leq$3 Gy and $\leq$5 Gy for right-sided and left-sided breast cancer, respectively, were kept strictly adhered to during internal mammary irradiation with either the VMAT or deep-inspiration breath-holding technique.[12] In addition, ipsilateral lung volume receiving $\geq$20 Gy was adhered <30% and <20% in the CF-3D and HF-3D groups, respectively.[12] Sequential

boost to the tumor bed was used in the CF-3D (73.6%) and HF-3D (86.7%) groups, with a total dose of 9 Gy in five fractions (CF-3D) or 10 Gy in five fractions (HF-3D), whereas simultaneous integrated boost (SIB) was performed in the HF-VMAT group (73.1%), with a total dose of 48 Gy in 15 fractions, similar to the RTOG 1005 protocol (Table S1). The RT dose for CF-3D and HF-3D was calculated with the Pinnacle Radiotherapy Planning System (Philips Medical System, Andover, MA); for HF-VMAT, this was calculated with the RayStation treatment planning system (version 5.0, RaySearch, Stockholm, Sweden). Figure S1 displays an example of CF-3D, HF-3D and HF-VMAT with or without RNI. Although all patients were treated at a single institution, dose-volume results for individual patients were not available due to limited information in the archiving planning data. Instead, we performed random selection evenly distributed across treatment eras (Table S2) to evaluate the dose parameters in each group. A simple random sample-by-sample function was performed, and individual cases for 480 patients (160 patients in each group) were analyzed. (Table S3). Kilovoltage cone-beam CT was used daily to verify the patient set-up and image guidance.

2.3 | Toxicities

The treating physicians assessed acute toxicities, including fatigue, esophagitis, breast pain, breast edema, induration and dermatitis, every week with the Common Terminology Criteria for Adverse Events (CTCAE version 4.03).[17] Subacute toxicities occurred within 1 month of RT completion. Physicians assessed breast edema, induration, skin dryness, hyperpigmentation and dermatitis during the 1-month follow-up. Late toxicities, such as symptomatic radiation pneumonitis (RP),[9] lymphedema,[18] hypothyroidism,[19] and cardiotoxicity,[20] were recorded by the treating physician. Symptomatic RP was defined as respiratory symptoms with correlated radiologic findings (CTCAE Grade ≥2). A physiatrist—specialized in cancer rehabilitation—conducted physical examinations and objective measurement to diagnose lymphedema.[18] Hypothyroidism after RT was diagnosed only on a new diagnosis of subclinical or clinical hypothyroidism. The endpoint of cardiotoxicity was ischemic heart disease with or without coronary revascularization, heart failure or death due to heart disease based on a medical chart review.

2.4 | Statistical analyses

The incidence of Grade 2+ acute/subacute toxicities and the time to late toxicity from RT initiation were the primary safety outcomes. The Pearson chi-squared or Fisher exact test was used to compare categorical variables, with the Student *t*-test or Mann-Whitney *U* test used for continuous variables. The rate of late toxicities was estimated using the Kaplan-Meier method. Logistic regression analysis was performed to evaluate the prognostic factors for acute/subacute toxicity; the Cox proportional hazards model was used for multivariable analysis of late toxicity. Because patients were not randomly assigned to the three treatment groups, propensity score inverse probability of treatment-weighted (IPTW) analysis was employed to minimize the effects of potential confounders and selection biases. Propensity scores were calculated using a multivariable logistic regression model including age, body mass index, hypertension, diabetes mellitus, smoking history, tumor laterality, tumor stage (T and N), surgery (breast-conserving surgery vs mastectomy), number of dissected nodes, chemotherapy (neoadjuvant/adjuvant, taxane−/anthracycline-based/trastuzumab), hormonal therapy, RNI and tumor bed boost. The appropriateness of each model was determined by using goodness-of-fit measurements (Table S4). Standardized mean differences were used to evaluate the balance of covariate distribution between two groups. Pairwise comparisons were performed using separate models after propensity score weighting. A Bonferroni-adjusted α-level of $P < .05/3$ (.0167) was considered statistically significant on pairwise comparisons; $P < .05$ was considered statistically significant in other analyses. All statistical analyses were performed using SAS (version 9.4, SAS Inc., Cary, NC) and IBM SPSS (Version 25.0; IBM Corp., Armonk, NY).

3 | RESULTS

Patient, tumor and treatment characteristics are summarized in Table S5. The mean age was 52.0 years; most patients were diagnosed with T1-2 ($N = 4353$, 75.7%) or N0 ($N = 4076$, 70.9%) disease. One-fifth of the patients (21.6%) received postmastectomy RT; more than half of the patients (64.0%) received adjuvant (50.1%) or neoadjuvant chemotherapy (23.0%). Unbalanced characteristics were adequately balanced for in each comparison (Table S6).

HF-VMAT resulted in the lowest rate of Grade 2+ acute toxicity (1.4% vs 14.0% and 2.2% after CF-3D and HF-3D, respectively; $P < .001$, Figure 1). HF-VMAT caused the lowest rates of Grade 2+ esophagitis and Grade 2+ dermatitis (Table 1). Subacute toxicities were also less frequent after HF-VMAT (0.1%) than after CF-3D (1.8%) and HF-3D (0.4%; Figure 1). HF-VMAT was less likely to cause Grade 2+ induration, hyperpigmentation and dermatitis (all <0.1%).

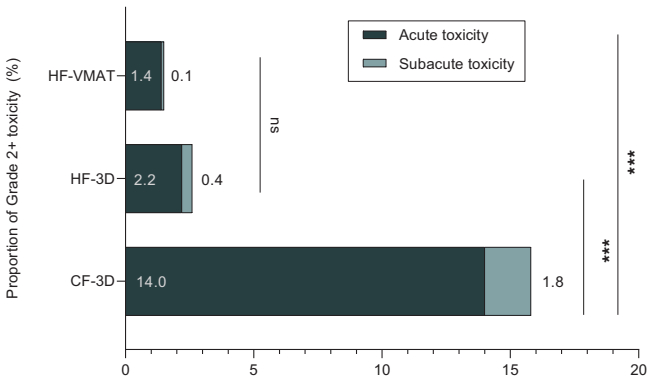

FIGURE 1 Rates of Grade 2 or more acute or subacute toxicity stratified by treatment group [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Radiation-related adverse events

Profiles	CF-3D N = 4209 N (%)	HF-3D N = 768 N (%)	HF-VMAT N = 772 N (%)	*P*
Any Grade ≥2	1523 (36.2)	102 (13.3)	110 (14.2)	<.001
Acute toxicity with any Grade ≥2	591 (14.0)	17 (2.2)	11 (1.4)	<.001
Fatigue				
Grade 1	307 (7.3)	77 (10.0)	54 (7.0)	.008
Grades 2 and 3	38 (0.9)	1 (0.1)	3 (0.4)	
Esophagitis				
Grade 1	69 (1.6)	7 (0.9)	12 (1.6)	.016
Grades 2 and 3	51 (1.2)	3 (0.4)	0 (0.0)	
Breast pain				
Grade 1	191 (4.5)	52 (6.8)	39 (5.1)	.059
Grades 2 and 3	27 (0.6)	3 (0.4)	2 (0.3)	
Breast edema				
Grade 1	10 (0.2)	17 (2.2)	9 (1.2)	<.001
Grades 2 and 3	8 (0.2)	0 (0.0)	0 (0.0)	
Induration				
Grade 1	25 (0.6)	9 (1.2)	17 (2.2)	<.001
Grades 2 and 3	7 (0.2)	0 (0.0)	1 (0.1)	
Dermatitis				
Grade 1	1647 (39.1)	504 (65.6)	358 (46.4)	<.001
Grade 2	458 (10.9)	10 (1.3)	4 (0.5)	
Grade 3	46 (1.1)	0 (0.0)	1 (0.1)	
Subacute toxicity with any Grade ≥2	76 (1.8)	3 (0.4)	1 (0.1)	<.001
Breast edema				
Grade 1	22 (0.5)	5 (0.7)	1 (0.1)	.401
Grades 2 and 3	4 (0.1)	0 (0.0)	0 (0.0)	
Induration				
Grade 1	34 (0.8)	15 (2.0)	5 (0.6)	.003
Grades 2 and 3	16 (0.4)	0 (0.0)	0 (0.0)	
Dryness				
Grade 1	103 (2.4)	22 (2.9)	28 (3.6)	.162
Grades 2 and 3	8 (0.2)	0 (0.0)	0 (0.0)	
Hyperpigmentation				
Grade 1	339 (8.1)	152 (19.8)	62 (8.0)	<.001
Grades 2 and 3	29 (0.7)	1 (0.1)	0 (0.0)	
Dermatitis				
Grade 1	341 (8.1)	197 (25.7)	92 (11.9)	<.001
Grade 2	34 (0.8)	2 (0.3)	0 (0.1)	
Grade 3	5 (0.1)	0 (0.0)	0 (0.0)	
Late toxicity	1077 (25.6)	84 (10.9)	99 (12.8)	<.001
Radiation pneumonitis	123 (2.9)	27 (3.5)	6 (0.8)	.001
Lymphedema	591 (14.0)	47 (6.1)	80 (10.4)	<.001
Hypothyroidism	207 (4.9)	3 (0.4)	6 (0.8)	<.001
Cardiotoxicity	288 (6.8)	13 (1.7)	8 (1.0)	<.001

Note: Values have been presented as numbers (percentages); *P* value<.05 is considered statistically significant.
Abbreviations: 3D, three-dimensional conformal radiation therapy; CF, conventional fractionation; HF, hypofractionation; VMAT, volumetric-modulated arc therapy.

After adjusting for clinical factors, HF-VMAT was significantly associated with fewer Grade 2+ acute/subacute toxicities than other modalities were (Table S7).

The median follow-up period of 38.4 (interquartile range [IQR], 29.3-49.0) months after HF-VMAT was significantly shorter than that for the other modalities (104.8 [IQR, 76.1-130.9] months and 49.2 [IQR, 39.2-60.0] months after CF-3D and HF-3D, respectively, $P < .001$). The 3-year cumulative rates for any late toxicities were 20.1%, 10.9% and 13.4% after CF-3D, HF-3D and HF-VMAT, respectively (Figure 2). Further analysis according to the late toxicity profiles (Figure S2) confirmed the superiority of HF-VMAT over CF-3D (hazard ratio [HR] 0.16) and HF-3D (HR 0.14), considering the incidence of RP (Table S8). HF-VMAT resulted in lower incidences of hypothyroidism (HR 0.26, Table S9) and cardiotoxicity (HR 0.37, Table S10) than CF-3D. The RT regimen did not influence the rate of lymphedema, although body mass index, the number of dissected

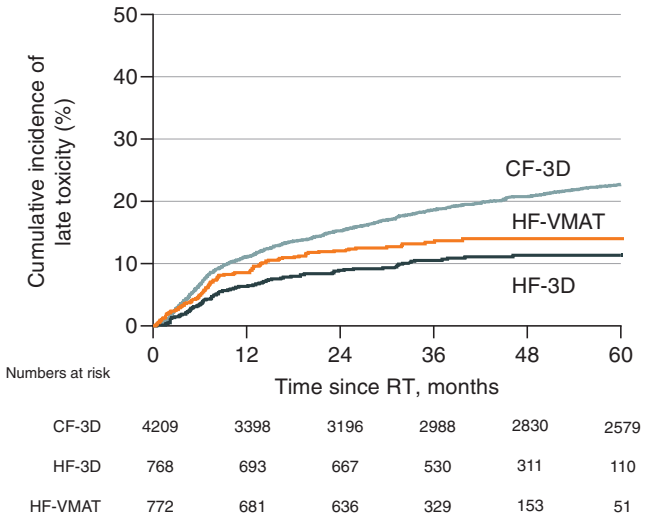

FIGURE 2 Cumulative incidence of late toxicity stratified by treatment group [Color figure can be viewed at wileyonlinelibrary.com]

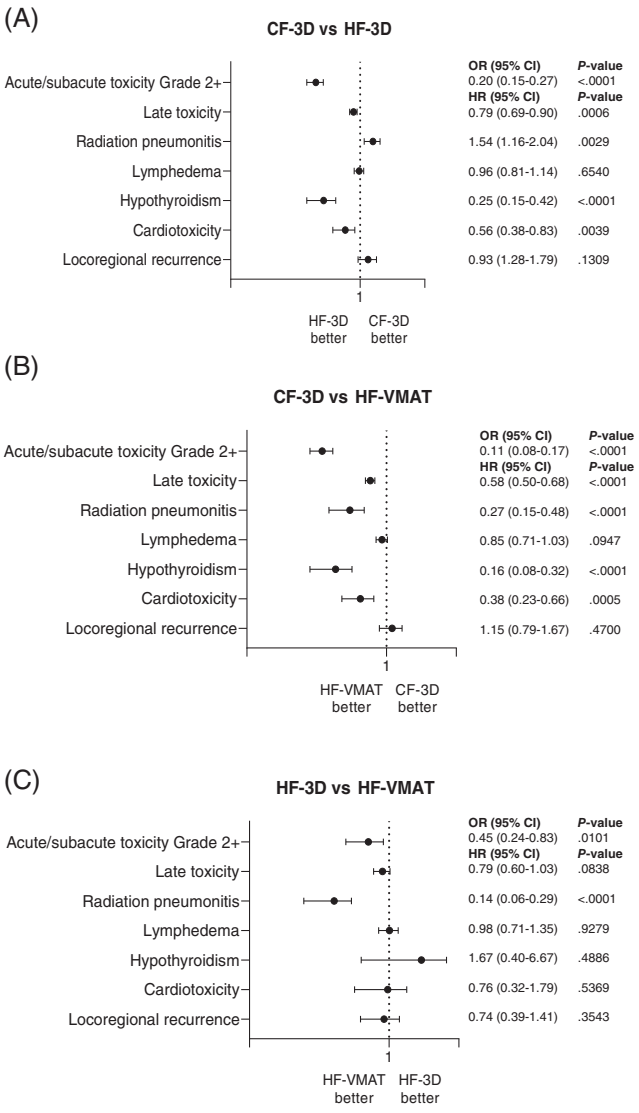

FIGURE 3 Forest plots of the pairwise comparison of toxicity by the treatment group after propensity score weighting: A, CF-3D vs HF-3D; B, CF-3D vs HF-VMAT; and C, HF-3D vs HF-VMAT

TABLE 2 Pairwise comparisons of outcomes by the treatment group after propensity score weighting

Outcome	CF-3D vs HF-3D (reference: CF-3D)		CF-3D vs HF-VMAT (reference: CF-3D)		HF-3D vs HF-VMAT (reference: HF-3D)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Acute or subacute toxicity with any Grade ≥2	0.20 (0.15-0.27)	<.001	0.11 (0.08-0.17)	<.001	0.45 (0.24-0.83)	.010
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Any late toxicity	0.79 (0.69-0.90)	.001	0.58 (0.50-0.68)	<.001	0.79 (0.60-1.03)	.084
Radiation pneumonitis	1.54 (1.16-2.04)	.003	0.27 (0.15-0.48)	<.001	0.14 (0.06-0.29)	<.001
Lymphedema	0.96 (0.81-1.14)	.654	0.85 (0.71-1.03)	.095	0.98 (0.71-1.35)	.928
Hypothyroidism	0.25 (0.15-0.42)	<.001	0.16 (0.08-0.32)	<.001	1.67 (0.40-6.67)	.489
Cardiotoxicity	0.56 (0.38-0.83)	.004	0.38 (0.23-0.66)	.001	0.76 (0.32-1.79)	.537
Locoregional recurrence	0.93 (1.28-1.79)	.131	1.15 (0.79-1.67)	.470	0.74 (0.39-1.41)	.354

Note: Values have been presented as odds ratios or hazard ratios with 95% confidence intervals; $P < .017$ is considered statistically significant.
Abbreviations: CF, conventional fractionation; 3D, three-dimensional conformal radiation therapy; HF, hypofractionation; VMAT, volumetric-modulated arc therapy; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

TABLE 3 Pairwise comparisons of outcomes by the treatment group after propensity score weighting stratified by regional node irradiation

No regional node irradiation	CF-3D vs HF-3D (reference: CF-3D)		CF-3D vs HF-VMAT (reference: CF-3D)		HF-3D vs HF-VMAT (reference: HF-3D)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Acute or subacute toxicity with any Grade ≥2	0.14 (0.08-0.22)	<.001	0.24 (0.16-0.38)	<.001	1.12 (0.48-2.62)	.785
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Any late toxicity	0.70 (0.56-0.88)	.002	0.45 (0.33-0.61)	<.001	0.71 (0.44-1.15)	.164
Radiation pneumonitis	0.91 (0.55-1.52)	.721	0.56 (0.28-1.14)	.110	0.27 (0.09-0.84)	.024
Lymphedema	0.86 (0.62-1.20)	.375	0.65 (0.43-0.99)	.044	1.14 (0.59-2.20)	.696
Hypothyroidism	0.20 (0.08-0.47)	.003	0.04 (0.00-0.38)	.006	0.76 (8.40-0.07)	.824
Cardiotoxicity	0.98 (0.64-1.48)	.911	0.50 (0.27-0.94)	.031	0.55 (0.19-1.55)	.257
Locoregional recurrence	0.83 (1.43-2.48)	.197	0.59 (0.24-1.47)	.256.	0.38 (0.10-1.45)	.155
Regional node irradiation	**CF-3D vs HF-3D (reference: CF-3D)**		**CF-3D vs HF-VMAT (reference: CF-3D)**		**HF-3D vs HF-VMAT (reference: HF-3D)**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Acute or subacute toxicity with any Grade≥2	0.24 (0.17-0.35)	<.001	0.03 (0.07-0.01)	<.001	0.15 (0.05-0.45)	.001
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Any late toxicity	0.77 (0.65-0.91)	.002	0.61 (0.51-0.74)	<.001	1.12 (0.58-0.80)	.199
Radiation pneumonitis	1.88 (1.33-2.66)	<.001	0.13 (0.05-0.34)	<.001	0.09 (0.03-0.29)	<.001
Lymphedema	0.88 (0.73-1.07)	.209	0.84 (0.69-1.03)	.089	0.91 (0.63-1.31)	.613
Hypothyroidism	0.27 (0.14-0.51)	<.001	0.24 (0.11-0.51)	<.001	2.61 (0.38-17.86)	.326
Cardiotoxicity	0.06 (0.01-0.30)	.001	0.25 (0.09-0.70)	.008	2.43 (0.46-12.82)	.298
Locoregional recurrence	1.09 (0.72-1.64)	.679	1.27 (0.83-1.93)	.271	0.97 (0.46-2.07)	.943

Note: Values have been presented as odds ratios or hazard ratios with 95% confidence intervals; $P < .017$ is considered statistically significant.
Abbreviations: CF, conventional fractionation; 3D, three-dimensional conformal radiation therapy; HF, hypofractionation; VMAT, volumetric-modulated arc therapy; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

nodes, taxane-based chemotherapy and comprehensive RNI covering axillary levels I to III were associated with lymphedema (Table S11).

Different models were used to compare the risk of toxic events (Table 2, Figure 3). Pairwise comparison demonstrated that HF-VMAT lowered the risk of Grade 2+ acute/subacute toxicity compared to CF-3D (odds ratio [OR] 0.11) and HF-3D (OR 0.45); the risk of Grade 2+ acute/subacute toxicity was lower after HF-3D than after CF-3D (OR 0.20). Grade 2+ late toxicities were more frequent after CF-3D than after HF-3D (HR 1.26) and HF-VMAT (HR 1.71). Specifically, fewer cases of RP, hypothyroidism and cardiotoxicity were observed after HF-VMAT than after CF-3D ($P < .001$). Moreover, RP was less frequent after HF-VMAT than after HF-3D (HR 0.45). All other late toxicities were comparable between HF-3D and HF-VMAT. Subgroup analysis according to RNI showed that both HF-3D and HF-VMAT decreased the risk of Grade 2+ acute/subacute toxicities regardless of RNI; the benefit of HF-VMAT over HF-3D was significant in patients who underwent RNI considering the incidence of RP (Table 3).

At the time of analysis, 139 of 4209 patients in the CF-3D group (3.3%) had locoregional tumor recurrences, as did 17 patients (2.2%) and 18 patients in the HF-3D and HF-VMAT groups (2.3%), respectively. The 5-year locoregional recurrence rates were 2.8%, 2.6% and 2.4% in the CF-3D, HF-3D and HF-VMAT groups, respectively. Pairwise comparison also showed comparable locoregional control rates among the groups (Table 2, Figure 3). The 5-year overall survival rates in the CF-3D, HF-3D and HF-VMAT groups were 95.5%, 97.4% and 95.3%, respectively.

4 | DISCUSSION

This large, retrospective, comparative analysis of a single-center cohort showed substantial differences in toxicities according to fractionation (CF vs HF) and techniques (3D vs IMRT). Moreover, this series represents the first large, homogeneous, single-center experience considering the efficacy and safety of VMAT and the practical proposal of adapted planning in different clinical situations (SIB with HF in 73.1% and RNI in 38.8%).

IPTW analysis revealed fewer acute/subacute and late toxic events after HF-RT than after CF-RT; even fewer acute/subacute toxicities were observed after HF-VMAT than after HF-3D, with comparable late toxicities. Our findings regarding the HF regimen are consistent with previous findings that fractionation of 40 Gy in 15 fractions is less harmful to normal tissues.[3] The 3-week schedule in the START-B trial had seemingly milder effects on normal tissue

than 50 Gy in 25 fractions.[3] Moreover, HF contributed to reduced toxicity in the current study in patients receiving RNI, similar to the pooled analysis data of 864 patients treated with RNI in the START trials.[3,5,21] The ongoing HYPOG-01 trial (NCT 03127995) will clarify whether the 15-fraction HF regimen shows fewer late toxicities (ie, lymphedema) than CF-RT.

Owing to limited toxicity, IMRT is used for breast cancer.[22,23] Among 331 patients with early breast cancer, the dose distributions were improved and moist desquamation was more reduced after IMRT than after the standard wedge technique (31% vs 48%).[22] Moreover, homogeneity within the breast from IMRT could minimize changes in breast appearance (by 0.59 times) and palpable induration compared to that observed with the two-dimensional technique (40% vs 58%).[23] However, limited data exist regarding the implementation of IMRT in HF-RT, making our findings regarding HF-VMAT novel.

VMAT—a new IMRT type and a potentially versatile solution—is applicable in various scenarios. VMAT is superior to other IMRT techniques considering target coverage, homogeneity, conformality and advantages in delivery.[24] The early results of clinical studies assessing 40 Gy in 15 fractions with VMAT seem promising, with fewer severe toxicities (0-8% of Grade 2 skin/lung toxicity; no Grade 3 toxicities).[24]

The reduced acute/subacute toxicities after HF-VMAT in only the RNI group after sensitivity analysis are important findings. Conventional techniques with wedges or forward planning make planning quite challenging for controlling the hot-spots <105% of the prescribed dose in RNI. For example, in the first phase II trial evaluating HF-RT in United States, a maximum 120% of the prescribed dose was allowed for <2 cc of the breast.[25] In contrast, HF-VMAT in the RNI group in the current study achieved a superior target coverage with a maximum dose of approximately 105% of the prescribed dose than that observed for 3D-RT. Owing to the higher fraction size in HF, hot-spots could be more clinically relevant in HF-RT than in CF-RT.

The treatment time reduced by 5 days after VMAT with SIB techniques as an alternative to sequential tumor bed boost performed in other groups. The tumor bed coverage was better after HF-VMAT (95-98%) than after CF-3D (89-93%) and HF-3D (81-96%). The SIB technique has been applied for breast cancer: 48 Gy in the RTOG 1005 trial and 48 or 53 Gy in the UK IMPORT HIGH trial. Importantly, HF-VMAT using the SIB technique did not compromise oncologic outcomes compared to CF-3D or HF-3D.

HF-VMAT was associated with reduced RP regardless of RNI. Our previous study showed that VMAT influenced RP; ipsilateral lung $V_{30\ Gy}$ > 10% was associated with RP (HR 2.89) and VMAT remained significant for determining the lung $V_{30\ Gy}$ (OR 0.12).[9] VMAT was also able to reduce the mean lung dose and lung volume exposed to 5 to 40 Gy in patients treated with internal mammary irradiation to a greater extent than 3D-RT with deep-inspiration breath-holding.[9] Significant differences were observed between HF-3D and HF-VMAT considering the ipsilateral lung dose in the current random samples.

As a median follow-up of 7.4 years (8.7 and 3.8 years for the CF and HF groups, respectively) is insufficient for assessing all potential late normal tissue effects (ie, cardiac damage, hypothyroidism and secondary malignancy), our findings considering cardiotoxicity should be interpreted cautiously. Institutional cardiac-sparing strategies have evolved gradually since 2013 and were more commonly adopted after HF than after CF. Moreover, 1-Gy increments in doses were associated with a 21% increase in major coronary events in patients treated between 2005 and 2013.[20] Therefore, individualized cardiac-sparing techniques might lead to a decreased risk of cardiac toxicity after HF-RT. However, long-term follow-up results are needed to warrant this hypothesis. As RNI usage is supported in high-risk patients,[26] radiation doses to the thyroid could influence the occurrence of clinical hypothyroidism.[27] Moreover, despite the extent of neck node coverage being associated with hypothyroidism,[19] rotational IMRT delivers a higher dose to the thyroid tissue than conventional techniques do. Therefore, stringent dose constraints to the thyroid can be considered without compromising target volume coverage for further HF-VMAT. However, HF-VMAT has little impact on the lymphedema risk even in patients receiving RNI, consistent with the long-term outcomes of the START trials.[21] In contrast, surgery or taxane-based chemotherapy or extended RNI that included axillary level I to III was associated with increased lymphedema risk, consistent with previous results.[18] Many radiation oncologists are reluctant to employ IMRT, especially VMAT, for patients with expected favorable survival outcomes, secondary to the low-dose spread throughout the thorax. Among 446 (7.8%) patients diagnosed with subsequent primary cancer after RT, 109 (2.6%), 9 (1.2%) and 9 (1.2%) patients experienced contralateral breast cancer in the CF-3D, HF-3D and HF-VMAT groups, respectively (Table S12). With a 5-year cumulative incidence of subsequent primary cancer of 4.7%, there was no difference among the treatment groups (Figure S3). Similarly, comparative analysis based on the National Cancer Database also revealed a comparable risk of secondary cancer after IMRT or 3D-RT.[28] However, longer surveillance should be warranted to demonstrate the safety of VMAT with regard to secondary cancer risk.

Apart from physicians' discretion, the cost-effectiveness of IMRT is an issue. Well-designed high-level, cost-effective analyses are required to convince the pragmatic decision-makers (ie, payers) where IMRT is substantially more expensive than conventional techniques (eg, United States). However, national consensus differs between countries, where the difference in cost is nuanced (eg, Canada and South Korea). As RT modalities continue to develop rapidly, variation in target delineation and RT planning is another issue.[29] Unless the quality of RT planning is strictly adhered to, the therapeutic ratio may diminish in real-world settings. Substantial variations in breast IMRT were observed considering the target volume, planning technique and dose to normal organs.[30]

The study has some limitations, including patient selection bias among the treatment groups owing to different utilization phases for each group. However, treatments were performed considering a consistent institutional policy; pairwise comparison with IPTW was performed to minimize bias. Moreover, the overall rate of toxicities might be slightly underestimated because only physician assessments were performed for analysis. Because a large breast volume can result in inhomogeneity and hot-spots during breast RT planning, the relatively

small-to-moderate size of breasts in Asian patients contributed to a lower rate of adverse events than that observed in Western patients. Hence, further assessment in Western patients using the three treatment groups is needed to validate the safety of HF-VMAT. Furthermore, reconstruction-related complications and late skin toxicity were not assessed. Finally, despite the consistent RT plans and techniques performed by well-experienced physicians who treat 500 patients per year at a single center, the analysis of individual radiation dose parameters was not feasible owing to a lack of data. However, an analysis of 480 patients (8.3% of the entire cohort) equally distributed across treatment era via random sampling showed that each RT plan in the treatment groups followed institutional dose-volume criteria. Further investigation incorporating individual plan results would better address the correlation between the dosimetric benefit of HF-VMAT and reduced treatment-related toxicity.

In conclusion, treatment with HF-VMAT using the 3-week schedule resulted in significantly improved RT-related toxicities than that observed for CF-3D and HF-3D, with comparable locoregional outcomes. The implementation of HF-VMAT could alleviate the severity of treatment-related toxicities, improving convenience for patients treated with protracted fractionation.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data availability is limited due to institutional data protection policies and confidentiality of patient data. Anonymized data that supports the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Health Institutional Review Board of Severance Hospital (No. 4-2020-0131). The requirement for informed consent was waived because of the retrospective nature of this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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