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Scientific Article

Volumetric Modulated Arc Therapy for 26 Gy in 5 Fractions Whole Breast Irradiation for Breast Cancer

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Purpose: To report the dosimetric and toxicity outcomes of patients treated with 26 Gy in 5 fractions ultrahypofractionated (uHF) whole breast irradiation (WBI) using volumetric arc therapy (VMAT).

Methods and Materials: We identified 476 consecutive patients who underwent WBI using VMAT-uHF between 2020 and 2021. Study endpoints included acute toxicity and dosimetric parameters for target volume and organs at risk. The dosimetric results were compared with a historical cohort at the same institution who were treated with moderately hypofractionated WBI using 3-dimensional (3D)-conformal radiation therapy (3D-CRT, n = 392), with the total dose rescaled to 26 Gy.

Results: VMAT-uHF achieved a mean D95% and Dmax of the planning target volume of 96.2% and 102.8% of the prescribed dose, respectively. The VMAT-uHF group demonstrated significantly superior planning target volume coverage and improved dose homogeneity, with a 30.6% higher D95 and a 0.7% lower Dmax compared with the 3D-CRT group (both $P < .05$). Mean doses for the ipsilateral lung and heart were 3.12 ± 4.59 Gy and 0.92 ± 0.25 Gy, respectively, showing differences of < 0.3 Gy compared with the 3D-CRT group. The VMAT-uHF group exhibited a significantly lower left anterior descending artery Dmax (−3.73 Gy), while the contralateral breast showed a higher Dmean (+1.43 Gy), compared with the 3D-CRT group. Acute toxicity following VMAT-uHF was predominantly mild, with grade 1 toxicity observed in 114 out of 120 patients. No additional toxicities were reported after a median follow-up of 21.2 months.

Conclusions: The application of VMAT in ultrahypofractionation can enhance target coverage while maintaining radiation doses to organs at risk low, albeit with an increase in contralateral breast dose compared with 3D-CRT. Given the low toxicity profile observed in our cohort with VMAT-uHF, the clinical significance of these dosimetric differences requires further investigation.

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The data accumulated throughout this study are available from the corresponding author (changjeesuk@yuhs.ac) upon reasonable request. Data sharing will only be available for academic research but not for other objectives (ie, commercial use). A data use agreement will be required before data release and institutional review board approval, as appropriate.

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Introduction

The recent phase 3 randomized Fast-Forward trial reported outcomes for over 4000 patients, comparing 26 and 27 Gy in 5 fractions over 1 week to 40 Gy in 15 fractions over 3 weeks.[1] After a 5-year follow-up, no significant difference in late breast toxicity was observed for the 26 of 5 regimen. The adoption of ultrahypofractionation (uHF) for whole breast irradiation (WBI) has increased substantially, with recent consensus recommendations from the European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee stating that uHF (26 Gy in 5 fractions) can be offered as the standard of care.[2] However, the 2024 National Comprehensive Cancer Network guidelines have yet to incorporate this regimen,[3] and hesitancy still exists among physicians and institutions regarding its implementation.[4,5] Although the authors of the Fast-Forward trial clarified that the third arm, delivering 27 Gy of WBI in 5 fractions, was equivalent to 50 Gy in 25 fractions in terms of late normal tissue effects, hesitance remains among physicians because of the significant impact of a 1 Gy difference in the total dose of the 5-fraction regimen on late normal tissue effects.[6]

Breast intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) is well-tolerated and has been reported to improve dose homogeneity, potentially minimizing radiation exposure to the heart and lungs.[7-9] Despite strong evidence supporting its effectiveness, the adoption of IMRT/VMAT for adjuvant breast radiation therapy (RT) varies internationally,[9,10] potentially influenced by resource availability, health policies, service models, and physician compensation.[8] While IMRT/VMAT can potentially mitigate concerns related to dose inhomogeneity and its impact on adverse effects in ultrahigh-dose fraction sizes, the application of IMRT/VMAT in the context of uHF has not been previously evaluated.

This study aimed to report dosimetric and acute toxicity outcomes for patients with early breast cancer treated with 26 Gy in 5 fractions (uHF) using VMAT and to compare the dosimetric outcomes of uHF with those of patients treated with 40 Gy in 15 fractions of moderately hypofractionated (mHF) using 3D-conformal RT (3D-CRT).

Materials and Methods

Study population

This study was approved by our institutional review board (No. 4-2023-1484). Our institution adapted a uHF regimen delivering 26 Gy in 5 fractions for patients scheduled to undergo WBI starting in June 2020, following the release of the Fast-Forward trial findings. In accordance with a national consensus recommending IMRT in breast RT for hypofractionation or when dosimetric goals are unmet, our institution has consistently used IMRT, with a preference for VMAT. All patients were treated with external-beam photon therapy using the VMAT technique. Therefore, we identified patients diagnosed with ductal carcinoma in situ or invasive early-stage breast cancer who underwent uHF WBI at our institution between June 2020 and December 2021 to evaluate the dosimetric results and early toxicity outcomes associated with uHF. Patients with a history of concurrent malignancies or those lost to follow-up were excluded (n = 34). A total of 476 patients treated with 26 Gy in 5 fractions of VMAT-uHF-WBI were included in this study. For dosimetric comparison, the control group was selected from patients with breast cancer who were treated with 40 Gy in 15 fractions of 3D-CRT-mHF-WBI from a previously reported data set,[11] because there were no patients at our institution treated with 3D-CRT-uHF-WBI.

VMAT-uHF

Patients were immobilized in a supine position with overhead arm positioners, without inclination, on a flat couch. Computed tomography (CT) simulation images were acquired in deep inspirational breath-hold (DIBH) using either the Abches system (Apex Medical Inc) or continuous positive airway pressure (Dreamstation CPAP & Bi-level, Philips) for patients with left-sided breast cancer to reduce the dose to the lung and heart. Based on the ESTRO consensus guidelines,[12] the clinical target volume (CTV), including CTV_breast and CTV_tumor bed, was contoured. The planning target volume (PTV) margin was expanded by 3 mm. PTV_breast was then cropped 3 to 5 mm inside the skin and the deep chest walls. The surgical tumor bed was defined based on preoperative CT/ultrasonographic images, surgical clips placed during surgery, postoperative seroma, simulation CT images, and surgical scars.

A prescription of 26 Gy in 5 fractions was administered to PTV breast, with dose objectives ensuring that 95% of the target volume received a minimum of 95% of the prescribed dose (V95% > 95%) while maintaining the maximum dose (Dmax) below 107%. Organ-at-risk (OAR) dose constraints were based on the Fast-Forward protocol[1]; V8% of the ipsilateral lung had to be <15%, D5 for the heart had to be < 7 Gy, and D30 had to be < 1.5 Gy (Table E1). Although the initial objectives were met, iterative refinement and adjustments are a common practice, resulting in treatment plans that surpass these objectives. A 2-partial-arcs VMAT plan was used. Additionally, we incorporated a ring-shaped virtual organ, approximately 2 to 3 cm from the PTV, to facilitate dose degradation during the optimization process. Following uHF-

WBI, a tumor bed boost of 10 Gy in 5 fractions was administered using VMAT planning. A daily cone-beam CT scan was used to assess interfraction motion during breast treatment. If significant discrepancies (eg, 5 mm in breast skin) were observed caused by changes in breast edema, resimulation was performed.

Control group: 3D-CRT-mHF (n = 390)

Patients planned for 3D-CRT were simulated in the supine position with DIBH (n = 113) for left-sided breast cancer, in the supine position without DIBH (n = 196), or in the prone position (n = 83) at the clinician's discretion. In 3D-CRT, planning typically does not involve the explicit contouring of breast CTV or PTV. A tangential-based approach using 2 primary radiation fields, the medial and lateral tangents, was employed for 3D-CRT planning. These were specifically angled to encompass the entire breast, outlined with radioopaque wires during CT simulation, or guided by bony landmarks. Manual adjustments (eg, multileaf collimator blocks based on the beam's eye view) were made to account for each patient's unique anatomy and to minimize doses to OARs such as the heart and lungs, using a 6 MV photon beam. The field-in-field technique was applied to enhance dose homogeneity and optimize target volume coverage, thereby reducing hotspots.

Plan analysis

Dose-volume histograms (DVHs) were used to analyze target volume coverage and doses to OARs. In the VMAT-uHF group, where sequential boost irradiation was used, a composite plan combining 2 plans was generated to assess doses to OARs; however, target volume coverage was evaluated based on the initial plan. Figure E1 demonstrates representative isodose distributions and DVH for the composite plan using the uHF regimen. In the 3D-CRT-mHF group, because breast CTV and PTV were generally not defined, they were retrospectively re-delineated in a blinded manner with respect to beam arrangements and dose distributions, following the ESTRO guidelines[12] and using a contouring approach similar to that of the VMAT-uHF group. Subsequently, the calculated dose distributions from the original 3D-CRT plans were transferred onto the newly contoured structures, and DVHs were evaluated for both target coverage and OAR doses. As the total dose in the 3D-CRT-mHF group differed, it was rescaled to a total dose of 26 Gy to ensure a fair comparison with VMAT-uHF.

We retrospectively collected dosimetric data for the target volume and OARs. This data encompassed maximum doses to the PTV, the percentage of the PTV receiving at least 95% of the prescribed dose, the maximum and mean doses to the contralateral breast, and the mean dose to the ipsilateral lung. Additional parameters included the mean doses to the contralateral lung and heart, the dose received by 10% of the heart volume, and the maximum and mean doses to the left anterior descending (LAD) artery.

Follow-up and evaluation

Toxicity was defined as the occurrence of physician-assessed, radiation-related acute toxicities, including fatigue, esophagitis, pain, edema, induration, and skin reactions, either during RT or within 6 months following its completion. These toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.03). Radiation-related acute toxicities were assessed weekly during treatment, 1 month after treatment, and at intervals of 3 to 6 months thereafter. Additionally, any other adverse events, as well as occurrences of ipsilateral breast tumor recurrence, regional recurrences, and distant metastases, were reviewed during the follow-up period.

Statistical analyses

The Pearson chi-squared test was used to compare categorical variables, and a *t* test was employed for continuous variables. All analyses were conducted on a per-breast basis. Logistic regression analysis was performed to identify predictive factors for acute toxicity. The multivariate analysis included variables with a *P* value below .1 in the univariate analysis. Follow-up duration and locoregional recurrence-free survival were calculated from the date of diagnosis to the date of the last visit or the date of recurrence, respectively. The significance level was set at 0.05, and all tests were 2-sided. All statistical analyses were conducted using IBM SPSS software (Version 27.0; IBM Corp).

Results

VMAT-uHF-WBI

We included 476 patients with ductal carcinoma in situ or invasive breast cancer treated with 26 Gy in 5 fractions of WBI using VMAT. Patient, tumor, and treatment characteristics are summarized in Table 1.

Figure 1 demonstrates representative isodose distributions of the uHF-VMAT WBI plan on axial and coronal CT images. The calculated PTV_whole breast volume averaged at 526.2 $\pm$ 10.8 cm^3. In the treatment plans, 95% and the maximum dose of the PTV received a mean of

Table 1 Patient characteristics of the VMAT-uHF group (n = 476)

Characteristic		No.	%
Age (y) (median = IQR)		53 (46-61)	
Laterality	Right	240	50.4
	Left	236	49.6
Pathology	DCIS	70	14.7
	IDC	326	68.5
	ILC	41	8.6
	Others	39	8.2
Pathologic T stage	T0/Tis/T1	417	87.6
	T2	59	12.4
Pathologic N stage	N0/N0mi	468	98.3
	N1	8	1.7
Molecular subtype per breast	Luminar A	217	45.6
	Luminar B	165	34.7
	HER2-positive	32	6.7
	Triple-negative	61	12.8
	Unknown	1	0.2
Chemotherapy	Yes	171	35.9
	Neoadjuvant	31	6.5
	Adjuvant	140	29.4
Taxane	Yes	51	10.7
Anthracycline	Yes	140	29.4
Trastuzumab*	Yes	53	73.6
Hormone therapy†	Yes	385	100
Boost RT	Yes	475	99.8

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IQR = interquartile range; PR = progesterone receptor; RT = radiation therapy; uHF = ultrahypofractionated radiation therapy (26 Gy in 5 fractions); VMAT = volumetric modulated arc therapy.
*Adjuvant trastuzumab therapy among 72 patients with HER2-positive breast cancer.
†Adjuvant hormone therapy among 385 patients with ER- or PR-positive breast cancer.

96.2% and 102.8% of the prescription dose, respectively. The mean doses of the ipsilateral lung and heart were 3.12 ± 4.59 and 0.92 ± 0.25 Gy, respectively. The remaining radiation doses to both target volumes and OARs are presented in Table 2.

All patients completed the planned treatment course without interruption. Physician-reported acute toxicity was observed in 120 (25.2%) patients with mostly mild toxicity (grade 1, 114/120) (Table 3). Acute dermatitis was the most common acute toxicity: 67 (14.1%) patients developed grade 1 while 2 (0.4%) had grade 2 skin reactions. Mild fatigue was reported in 22 (4.6%) patients, followed by grade 1 or 2 breast pain in 18 (3.8%) patients, and grade 1 or 2 breast edema in 11 (2.3%) patients. With a median follow-up of 21.2 months (interquartile range, 18.9-25.6 months), no other toxicities were observed. One patient developed regional nodal recurrence, and 1 had a distant metastasis during the follow-up period.

In univariate and multivariate analyses, age ≥53 years was independently associated with a lower incidence of any-grade acute toxicity (vs <53 years, adjusted HR, 0.52; 95% CI, [0.34-0.80], $P = .003$) (Table 4).

Dosimetric comparison with the 3D-CRT-mHF control group

We performed a dosimetric comparison between VMAT-uHF and 3D-CRT-mHF, with the 3D-CRT group rescaled to 26 Gy for fair comparison (Table 2). The control group consisted of 392 patients with 40 Gy in 15 fractions, all planned and delivered using the 3D-CRT technique. Figure E2 displays an example of a 3D-CRT-mHF-WBI plan.

The PTV volumes were comparable between the 2 groups. However, the VMAT-uHF group demonstrated significantly superior PTV coverage, with a 30.6% higher D95, while Dmax was 0.7% lower compared with the 3D-CRT-mHF group (both $P < .05$). Notably, the contralateral breast exhibited higher Dmax and Dmean in the VMAT-uHF group, with differences of +5.28 and +1.43 Gy, respectively. In contrast, the VMAT-uHF group demonstrated lower LAD artery Dmax and Dmean, with differences of −3.73 and −0.57 Gy, respectively. No statistically significant differences were observed in ipsilateral lung Dmean or Heart D10 between the 2 techniques. Other OAR variables, including heart Dmean, showed statistically significant differences; however, these differences were generally < 0.5 Gy.

Discussion

This study aimed to investigate the use of VMAT in the uHF regimen, which was previously tested using the 3D-CRT technique in the UK Fast-Forward trial. Table 5[13–19] summarizes the recent literature on uHF with either the 3D-conformal technique or IMRT/VMAT following the publication of the Fast-Forward or Fast trials reports. To the best of our knowledge, this is the largest report to date on the use of VMAT in uHF-WBI.[13-16] In the UK Fast-Forward trial, dose constraints for the uHF arms included > 95% of the volume receiving 95% of the prescribed dose, < 5% receiving ≥ 105%, < 2% receiving ≥ 107%, and a global maximum of < 110%.[1] The Fast-Forward trial's RT quality assurance program revealed that most

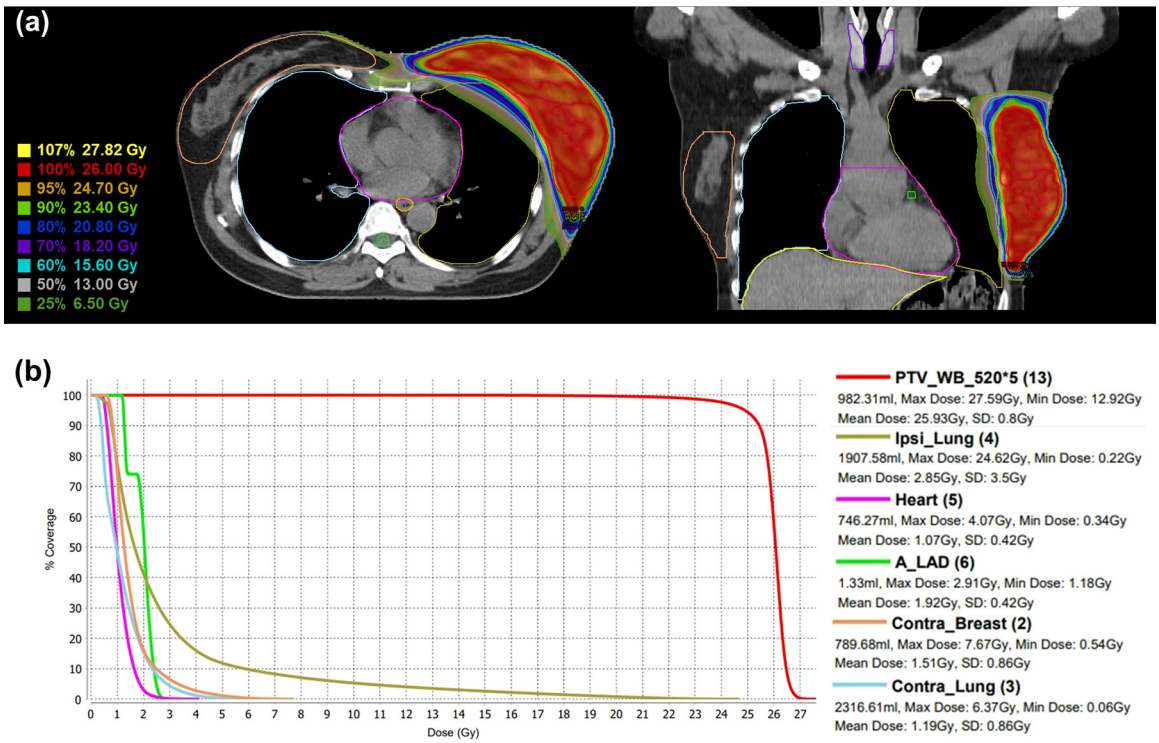

Figure 1 Isodose distribution and dose-volume histogram (DVH) for a case of left-sided breast cancer treated with ultrahypofractionated whole breast irradiation (uHF-WBI) using the volumetric modulated arc therapy (VMAT) technique. (a) isodose distribution and (b) DVH for WBI (26 Gy in 5 fractions). PTV_whole breast D95% 95.77%; PTV_whole breast Dmax 106.12%; Heart V1.5Gy 14.94%, V7Gy 0%, Dmean 1.07 Gy; LAD artery Dmean 1.92 Gy; Ipsilateral lung V8Gy 7.06%; contralateral lung D10 2.33 Gy; contralateral breast D5 3.31 Gy.

Abbreviations: Dmax (%) = maximum dose to the target volume/prescribed dose to the target volume; Dmean (Gy) = average dose to the target volume; LAD = left anterior descending; PTV = planning target volume.

plans (97.3%) complied with these dose objectives while only a few (1.5%) exceeded the V105% and V107% tolerances.[17] These criteria were consistently met in our study. Furthermore, the use of VMAT resulted in significant improvements in dose homogeneity within target volumes, achieving a maximum dose of 102.8% ± 1.9%. This value is considerably lower than the 105.5% (range, 104%-109.2%) observed in the RT quality assurance analysis of the Fast-Forward trial,[20] as well as the 106.3% (range, 103.1%-108.5%) reported for 133 patients treated with uHF (5.7 Gy once a week for 5 weeks) using a 3D technique in a study by Zerella et al[21] This discrepancy may be explained either by our practice, which involves iterative refinement and adjustments despite fulfilling initial objectives—resulting in plans that exceed these objectives. Since there is a well-established relationship between dose inhomogeneity (eg, 2-dimensional vs 3D breast dosimetry) and RT-related adverse effects,[8] we believe that further research is warranted to investigate whether improvements in dose inhomogeneity, achieved by incorporating VMAT, could translate into meaningful clinical benefits.

In the Fast-Forward protocol, a field-based structure, which is not a true PTV, was used.[1] Specifically, this field-based PTV was generated after selecting a tangential field pair, with margins extending 5 mm beyond the skin surface, 5 mm beyond the lung/chest wall interface, 5 mm beyond the posterior beam edge, and 10 mm beyond the superior and inferior beam edges. Because 3D-CRT planning during our study period did not typically involve explicit contouring of breast CTV or PTV, we retrospectively delineated new CTV and PTV structures for this study. The comparable PTV volumes in the 3D-CRT group provide reassurance that both groups were evaluated using true PTVs. Our findings revealed that 3D-CRT plans appeared suboptimal in target coverage when evaluated against IMRT standards. If a similar field-based PTV had been generated for the 3D-CRT plans, the PTV coverage would likely have been higher than observed in the current results. Conversely, this suggests that 3D-CRT planning may underestimate the whole breast volume compared with IMRT planning. The slightly higher contralateral breast dose in VMAT may partly

Table 2 Dose-volume histogram metrics of VMAT-uHF versus 3D-CRT-mHF with the 3D-CRT-mHF group rescaled to 26 Gy

Variables	VMAT-uHF (n = 476) mean ± SD	3D-CRT-mHF (n = 390) mean ± SD	Mean difference
PTV_whole breast volume (cc)	526 ± 235	555 ± 303	
PTV_whole breast D_{95} (%)	96.2 ± 1.0	65.6 ± 25.0	+30.6*
PTV_whole breast D_{max} (%)	102.8 ± 1.9	103.5 ± 3.1	−0.7*
Ipsilateral lung D_{mean} (Gy)	3.12 ± 4.59	3.37 ± 1.56	−0.25
Heart D_{mean} (Gy)	0.92 ± 0.25	0.76 ± 0.34	+0.16*
Heart D_{10} (Gy)	1.50 ± 0.49	1.50 ± 0.66	0
LAD artery D_{max} (Gy)	2.39 ± 1.61	6.12 ± 5.76	−3.73*
LAD artery D_{mean} (Gy)	1.30 ± 0.61	1.87 ± 1.53	−0.57*
Contralateral breast D_{max} (Gy)	8.90 ± 6.89	3.62 ± 4.46	+5.28*
Contralateral breast D_{mean} (Gy)	1.72 ± 4.89	0.29 ± 0.12	+1.43*
Left-sided			
Ipsilateral lung D_{mean} (Gy)	3.19 ± 6.49	2.69 ± 1.50	+0.50
Heart D_{mean} (Gy)	0.96 ± 0.26	0.97 ± 0.32	−0.01
Heart D_{10} (Gy)	1.56 ± 0.58	1.90 ± 0.60	−0.34*
LAD artery D_{max} (Gy)	3.47 ± 1.55	9.35 ± 4.88	−5.88*
LAD artery D_{mean} (Gy)	1.70 ± 0.55	2.72 ± 1.31	−1.02*
Right-sided			
Ipsilateral lung D_{mean} (Gy)	3.06 ± 0.66	4.12 ± 1.26	−1.06*
Heart D_{mean} (Gy)	0.89 ± 0.23	0.53 ± 0.17	0.36*
Heart D_{10} (Gy)	1.44 ± 0.36	1.07 ± 0.39	0.37*
LAD artery D_{max} (Gy)	1.34 ± 0.73	0.55 ± 0.22	0.79*
LAD artery D_{mean} (Gy)	0.90 ± 0.36	0.39 ± 0.14	0.51*

Abbreviations: 3D = 3-dimensional conformal radiation therapy; Dmax (Gy) = maximum dose to the target volume; Dmax (%) = maximum dose to the target volume/prescribed dose to the target volume; Dmean (Gy) = average dose to the target volume; Dmean (%) = average dose to the target volume/prescribed dose to the target volume; Dx (Gy) = minimum dose delivered to x% of the target volume; Dx (%) = minimum dose delivered to x% of the target volume/prescribed dose to the target volume; LAD = left anterior descending; mHF = moderately hypofractionated radiation therapy (40 Gy in 15 fractions); PTV = planning target volume; SD = standard deviation; uHF = ultrahypofractionated radiation therapy (26 Gy in 5 fractions); VMAT = volumetric modulated arc therapy; Vx (%) = percentage volume receiving more than × Gy.
*All comparisons were statistically significant ($P < .05$).

result from its more comprehensive coverage of the medial portion of the whole breast volume compared with 3D-CRT.

The detection of late events, such as cardiac incidents[22] and secondary lung cancer,[21] requires extended follow-up periods. As a result, dose-volume parameters for lung and heart structures have been employed as proxies for risk estimation. In the current study, VMAT-uHF demonstrated that for both left- and right-sided tumors, the volumes of the ipsilateral lung and heart receiving 10 Gy—6.6% ± 2.2% and 1.65% ± 0.6% for left-sided, 7.3% ± 2.5% and 1.4% ± 0.4% for right-sided, respectively—were significantly below the Fast-Forward protocol's dose constraints.[1] Significant PTV undercoverage in the 3D-CRT group can partly explain the lack of superiority of the VMAT technique in sparing lung and heart doses. Importantly, despite the use of prone positioning and DIBH planning when clinically indicated in 3D-CRT, VMAT demonstrated significantly lower LAD Dmax and Dmean. This finding is clinically significant, given the results of Zureick et al[23], who reported a notable increase in adverse cardiac events when LAD Dmean exceeded 2.8 Gy or LAD Dmax exceeded 6.7 Gy.

A report from the Fast-Forward trial suggested that erythema following the 1-week schedule was less intense and resolved approximately 2 weeks earlier than after the 3-week schedule, primarily caused by reductions in the total dose.[24] The proportion of worst acute Common Terminology Criteria for Adverse Events (version 4.03) toxicity for the 26 Gy per 5

Table 3 Acute toxicity following VMAT-uHF (n = 476)

Parameters	Grade	No.	%
Acute toxicity (any grade)		120	25.2
Acute toxicity (≥ grade 2)		6	1.3
Fatigue	0	454	95.4
	1	22	4.6
	2	0	0
Pain	0	458	96.2
	1	15	3.2
	2	3	0.6
Edema	0	465	97.7
	1	10	2.1
	2	1	0.2
Induration	0	475	99.8
	1	1	0.2
	2	0	0
Esophagitis	0	476	100
	1	0	0
	2	0	0
Dermatitis	0	407	85.5
	1	67	14.1
	2	2	0.4
Others	0	464	97.5
	1	12*	2.5
	2	0	0

Abbreviations: uHF = ultrahypofractionated radiation therapy (26 Gy in 5 fractions); VMAT = volumetric modulated arc therapy.
*Grade 1 anorexia in 8 patients and grade 1 nausea in 4 patients.

fraction arm was 0% for grade 3, 36% for grade 2, and 58% for grade 1. Among the grade 1 toxicities, the majority were cases of faint erythema. Although the evaluation was not prospective in the current study, instances of grade 2 and grade 1 toxicity were extremely rare (0.4% and 14.1%, respectively) in this VMAT-uHF cohort. Most patients (85.5%) experienced almost no skin changes and exhibited no moist desquamation reactions. Moreover, similar to the findings of the previous Fast-Forward trial,[24] our study demonstrated that the incidence of skin reactions was significantly lower in the uHF regimen compared with 3D-CRT mHF (14.5% vs 69.4%). While the study by Tsang et al[25] showed that dose inhomogeneity had no significant impact on late normal tissue events within 3D dosimetry in uFH regimen, our findings suggest the hypothesis that the established benefits of IMRT in breast RT,[7,22,25,26] may be even more pronounced in the context of uHF.

Our study had several limitations, including its single-institution and retrospective nature. A primary limitation of this study is the absence of a 3D-CRT-uHF comparison group because this regimen was not used at our institution. Thus, direct toxicity comparisons between 3D-CRT and VMAT in a 5-fraction setting were not possible. However, prior research on 4209 patients showed that VMAT reduced grade 2+ acute, subacute, and late toxicities compared with 3D-CRT in a 15-fraction setting.[11] Given the retrospective nature of this study, the toxicity profile reported here is likely to be underreported compared with the findings of the Fast-Forward trial. Given that breast size is an established factor for increased adverse effects following breast RT,[27] the relatively small breast size and single ethnicity of the present cohort (median PTV volume, 489.5 cm^3; interquartile range, 347.6-653.3 cm^3) should be considered while interpreting our results. Moreover, unlike the low use of boost RT (24.3%) in the Fast-Forward trial,[1] its routine use in our study should be considered, because OAR doses would likely have been lower if boost RT were omitted. Perspectives on the necessity of longer follow-up, cost, and treatment resources for IMRT or uHF, which vary across countries and institutions, should be considered when interpreting our findings.[28–30] Lastly, it is important to

Table 4 Univariate and multivariate analyses identifying factors associated with acute toxicity (n = 476)

Variables	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥53 y vs <53 years)*	0.50	0.33-0.77	.001	0.52	0.34-0.80	.003
Laterality (left vs right)	0.72	0.47-1.08	.114			
Molecular subtype (luminal type vs others)	0.72	0.44-1.31	.328			
Neoadjuvant CTx (yes vs no)	0.70	0.28-1.74	.440			
Adjuvant CTx (yes vs no)	0.62	0.39-1.01	.056	0.68	0.42-1.11	.127
Hormone therapy (yes vs no)	1.25	0.72-2.15	.430			
PTV volume (≥ 494.61 vs < 494.61 cc)*	0.80	0.53-1.21	.292			

Abbreviations: CI = confidence interval; CTx = chemotherapy; HR = hazard ratio; PTV = planning target volume.
*Median values of age and PTV volume were calculated for all patients.

Table 5 Summary of recent literature on ultrahypofractionated radiation therapy following the publication of the FAST-Forward trial

First authors	Year	n	Age (y)	Tumor volume	RT dose-fractionation	Boost RT	RT technique	PTV D95%	PTV Dmax	RT-related acute toxicity
Current study	2023	426	median 54 (46-61) y	PTV median 526.2 cc	26 Gy in 5 fractions (daily)	99.8%	VMAT	96.2% ± 1.0%	102.8% ± 1.9%	G2 1.3% (breast pain 0.6% = dermatitis 0.4% = edema 0.2%) = no G3+
Nugent et al[17]	2023	135	60-69 y 37% = >70 y 33%	Not reported	26 Gy in 5 fractions (daily)	28%	3D-CRT	median 96.3%	median 105.5%	G2 skin 32% = no G3+
Zerella et al[18]	2022	271	median 76 (46-86) y	Small (< 500 cc) 35.8% = medium (500-1000 cc) 48.7% = large (> 1000 cc) 15.5%	28.5 Gy in 5 fractions (weekly for 5 wk)	0%	3D-CRT 49% = IMRT 51%	≥ 95%	3D median 106.3% = IMRT median 106.4%	G2 15.5% = G3 0.4% (only erythema)
Akhtaruzzaman et al[19]	2023	10	median 48 (25-73) y	Not reported	26 Gy in 5 fractions (daily)	0%	VMAT	mean 97.8% ± 1.1% (FF) = 96.5% ± 0.8% (FFF)	mean 109.4% ± 1.0% (FF) = 108.6% ± 1.3% (FFF)	Not reported
Naziri et al[14]	Abst (2022)	47	median 65 y	median 1.4 cm	26 Gy in 5 fractions (daily)	91.5%	VMAT	Not reported	Not reported	Patients reported QOL: quite a bit or very much fatigue = breast pain = skin problems = and rash in 14.9% = 10.6% = 12.8% = and 6.4%. Satisfied in 97.9%
Othman et al[13]	Abst (2022)	188	median 60.5 y	Not reported	26 Gy in 5 fractions (daily)	26%	Not reported	Not reported	Not reported	G2 5% = no G3+
Montero et al[15]	2022	383	median 56 (30-99) y	PTV median 725 cc	26 Gy in 5 fractions (daily) 71% = concomitant boost 30-31 Gy in 5 fractions 29%	71%	3D-CRT 96% = VMAT 4%	Not reported	Not reported	G2 dermatitis 4% = G2 breast edema 0.5% = no G3+
Sigaudi et al[16]	2022	70	median 67 y (26 Gy group) = 70 y (28.5 Gy group)	PTV mean 531.4 cc (26 Gy group) = 532.9 cc (28.5 Gy group)	26 Gy in 5 fractions (Daily) 84% = 28.5 Gy in 5 fractions (weekly for 5 wk) 16%	Not reported	Static IMRT	mean 96.5% (26 Gy group) = 96.6% (28.5 Gy group)	D2 mean 1.0% (26 Gy group) = 1.0% (28.5 Gy group)	G2 erythema 6.7% = G2 induration 4.4% = no G3+

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; FF = flattening filter; FFF = flattening filter free; IMRT = intensity modulated radiation therapy; RT = radiation therapy; PTV = planning target volume; QOL = quality of life; VMAT = volumetric modulated arc therapy.

note the need for actual long-term data concerning ipsilateral breast tumor recurrence, secondary malignancies, and late toxicity outcomes.

Conclusion

Our findings suggest that VMAT in ultrahypofractionation provides improved target coverage while maintaining low radiation exposure to OARs, though it is associated with an increased contralateral breast dose compared with 3D-CRT. Notably, the significant reduction in LAD dose with VMAT warrants closer attention, even as the clinical relevance of these dosimetric differences remains to be elucidated. While VMAT-uHF demonstrated low toxicity outcomes at 21 months, long-term follow-up and prospective studies are crucial to validate these results.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2025.101733.

References

1. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613-1626.
2. Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. *Lancet Oncol*. 2022;23:e21-e31.
3. *NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 6*. 2024.. Accessed December 26, 2024; https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419.
4. Corrigan KL, Lei X, Ahmad N, et al. Adoption of ultrahypofractionated radiation therapy in patients with breast cancer. *Adv Radiat Oncol*. 2022;7:100877.
5. Mushonga M, Weiss J, Liu ZA, et al. Hypofractionation in breast cancer radiotherapy across World Bank income groups: Results of an international survey. *JCO Glob Oncol*. 2023;9:e2200127.
6. Brunt AM, Haviland JS, Kirby AM, et al. Five-fraction radiotherapy for breast cancer: FAST-Forward to implementation. *Clin Oncol (R Coll Radiol)*. 2021;33:430-439.
7. Choi KH, Ahn SJ, Jeong JU, et al. Postoperative radiotherapy with intensity-modulated radiation therapy versus 3-dimensional conformal radiotherapy in early breast cancer: A randomized clinical trial of KROG 15-03. *Radiother Oncol*. 2021;154:179-186.
8. Chang JS, Chang JH, Kim N, Kim YB, Shin KH, Kim K. Intensity modulated radiotherapy and volumetric modulated arc therapy in the treatment of breast cancer: An updated review. *J Breast Cancer*. 2022;25:349-365.
9. Aristei C, Kaidar-Person O, Boersma L, et al. The 2022 Assisi Think Tank Meeting: White paper on optimising radiation therapy for breast cancer. *Crit Rev Oncol Hematol*. 2023;187:104035.
10. theMednet. *What percentage of your breast cancer patients do you plan using IMRT vs 3D?* Accessed August 30, 2023. https://www.themednet.org/question/17354?var_gccgqd_id=16669799&notification_id=4636d2ff58c7decc9d295f74e0db4f9516e13c44&question_id=17354&update_id=66461&poll=1.
11. Kim N, Chang JS, Shah C, et al. Hypofractionated volumetric-modulated arc therapy for breast cancer: A propensity-score-weighted comparison of radiation-related toxicity. *Int J Cancer*. 2021;149:149-157.
12. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol*. 2015;114:3-10.
13. Othman H, Koch A, Purdie TG, et al. Early institutional experience of ultra-hypofractionated breast radiotherapy in a large academic cancer center. *Int J Radiat Oncol Biol Phys*. 2022;114:e21.
14. Naziri J, Miyani D, Luera-Sanchez M, et al. Patient reported quality of life outcomes and patient satisfaction of 1-week hypofractionated whole breast radiation therapy using imrt for early-stage breast cancer. *Int J Radiat Oncol Biol Phys*. 2022;114:e20.
15. Montero A, Ciervide R, Canadillas C, et al. Acute skin toxicity of ultra-hypofractionated whole breast radiotherapy with simultaneous integrated boost for early breast cancer. *Clin Transl Radiat Oncol*. 2023;41:100651.
16. Sigaudi V, Zannetti M, Ferrara E, et al. Ultra-hypofractionation for whole-breast irradiation in early breast cancer: Interim analysis of a prospective study. *Biomedicines*. 2022;10:2658.
17. Zotova R, Yarnold J, Wheatley D, Griffin C, Murray B. PD-0430: Results from the radiotherapy quality assurance programme for the FAST-Forward breast trial. *Radiat Oncol*. 2015;115:S209-S210.
18. Zerella MA, Dicuonzo S, Frassoni S, et al. Ultra-hypofractionated whole breast adjuvant radiotherapy in the real-world setting: Single experience with 271 elderly/frail patients treated with 3D and IMRT technique. *J Cancer Res Clin Oncol*. 2022;148:823-835.
19. Akhtaruzzaman M, Islam MJ, Mannan MA, Sumon MA, Ebert M. Delivery of a VMAT technique with flattening filter (FF) and flattening filter free (FFF) mode for whole breast irradiation with five fractions (FAST-Forward trial). *Med Dosim*. 2023;48:211-215.
20. Nugent K, Quinlan E, Cleary S, et al. Implementation of 26 Gy in five fractions over 1 week adjuvant radiotherapy for breast cancer: Prospective report of acute skin toxicity and consideration of resource implications. *Breast*. 2023;67:55-61.
21. Pignol JP, Hoekstra N, Wilke D, Dahn H, Nolan M, Vicini F. Estimation of annual secondary lung cancer deaths using various adjuvant breast radiotherapy techniques for early-stage cancers. *Front Oncol*. 2021;11:713328.
22. Chung SY, Oh J, Chang JS, et al. Risk of cardiac disease in patients with breast cancer: impact of patient-specific factors and individual heart dose from three-dimensional radiation therapy planning. *Int J Radiat Oncol Biol Phys*. 2021;110:473-481.

23. Zureick AH, Grzywacz VP, Almahariq MF, et al. Dose to the left anterior descending artery correlates with cardiac events after irradiation for breast cancer. *Int J Radiat Oncol Biol Phys*. 2022;114:130-139.
24. Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol*. 2016;120:114-118.
25. Tsang Y, Haviland J, Venables K, Yarnold J, Group FTM. The impact of dose heterogeneity on late normal tissue complication risk after hypofractionated whole breast radiotherapy. *Radiother Oncol*. 2012;104:143-147.
26. Pignol JP, Hoekstra N, Wilke D, Dahn H, Nolan M, Vicini F. Estimation of annual secondary lung cancer deaths using various adjuvant breast radiotherapy techniques for early-stage cancers. *Frontiers in Oncology*. 2021;11:713328.
27. Ratosa I, Jenko A, Oblak I. Breast size impact on adjuvant radiotherapy adverse effects and dose parameters in treatment planning. *Radiol Oncol*. 2018;52:233-244.
28. Halasz LM, Patel SA, McDougall JA, et al. Intensity modulated radiation therapy following lumpectomy in early-stage breast cancer: Patterns of use and cost consequences among Medicare beneficiaries. *PLoS One*. 2019;14:e0222904.
29. Smith GL, Smith BD. Sea change: A decade of intensity-modulated radiation therapy for treatment of breast cancer. *J Natl Cancer Inst*. 2020;112:221-223.
30. Lee JE, Yang K, Ahn YC, Park W, Huh SJ. Recent trends of medical expenses associated with radiation therapy in Korea based on HIRA big data. *Cancer Res Treat*. 2023;55:758-765.