Safety of hypofractionated volumetric modulated arc therapy for early breast cancer: A preliminary report

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Abstract. The present study attempts to evaluate the acute and subacute toxicities of hypofractionated volumetric modulated arc therapy (HFX-VMAT) in patients with early breast cancer (EBC). It is a retrospective analysis of 23 patients treated with HFX-VMAT after breast-conserving surgery between September 2021 and February 2022. A total dose of 50.05 to 52.55 Gy was delivered, consisting of 40.05 Gy to the ipsilateral whole breast in 15 fractions of 2.67 Gy and a tumor bed boost dose of 10-12.5 Gy in 4-5 fractions. The primary endpoint was acute/subacute radiation pneumonitis (RP). The secondary endpoint was poor cosmesis, indicating acute/subacute radiation dermatitis. Chest computed tomography (CT) and the Common Terminology Criteria for Adverse Events v.5.0 were used to assess acute and subacute RP and dermatitis, respectively, during radiotherapy (RT) and at 3- and 6-months post-RT. The median follow-up duration was 3.8 months (range, 2.3-4.2). A total of seven patients developed RP. None of these patients presented RP-related symptoms; the diagnosis was based on radiologic findings observed on follow-up chest CT. Among the seven patients with RP, five had right-sided, and two had left-sided breast tumors (71.4 vs. 28.6%; P=0.026). Grade 1 erythema was observed in 19 patients (82.6%) and grade 2 erythema in four (17.4%). The mean target dose, $D_{105\%}$ (the dose received by 105% of the target volume), homogeneity index, mean lung dose, ipsilateral lung V_{20} (the percentage volume receiving 20 Gy), and V_{30} (the percentage volume receiving 30 Gy) for ipsilateral whole breast RT were significantly associated with RP (P=0.039, 0.047, 0.018, 0.015, 0.018 and 0.003, respectively.). HFX-VMAT showed tolerable acute/subacute toxicities. Therefore, HFX-VMAT is an effective and safe treatment option for EBC.

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Introduction

Breast-conserving surgery followed by breast irradiation has become the standard therapy for patients with early breast cancer (EBC) (1). In 3-dimensional conformal radiotherapy (3DCRT), tangentially opposed beams deliver radiation to the ipsilateral whole breast. However, ipsilateral whole breast irradiation results in acute toxicities to organs at risk (OAR), such as the ipsilateral lung and heart (2). As such, considerable efforts have been made to minimize the irradiation dose to adjacent normal tissues to avoid acute and long-term adverse effects in patients with breast cancer.

Recently, the paradigm of radiotherapy (RT) for patients with EBC has been changing from conventional 3DCRT to hypofractionated (HFX) intensity-modulated radiation therapy (IMRT). HFX-IMRT, including volumetric modulated arc therapy (VMAT), can improve the accuracy of radiation delivery. In addition, HFX-RT can shorten the duration of RT, which is highly beneficial to patients (3). HFX-RT also has comparable results to conventional RT regarding local control rate and skin toxicity (4-7). Existing studies (4,5,8-11), which include the treatment results of various RT techniques, fields, or doses, demonstrate that despite the improvement in RT technology, there are still concerns about the side effects on adjacent normal organs. Therefore, the present study aimed to analyze the acute and subacute RT toxicities of patients with EBC who underwent breast-only HFX-VMAT at a single institution. It also investigated the prognostic factors of radiation physics related to radiation pneumonitis (RP) and dermatitis.

Materials and methods

Patients. The present study included 23 patients who underwent breast-conserving surgery and HFX-VMAT between September 2021 and February 2022 at Hanyang University Hanmaeum Changwon Hospital (Changwon, South Korea). The inclusion criteria were as follows: i) Histologically confirmed invasive breast cancer; ii) EBC with pathologic tumor (T) staging of Tis to T2 and node-negative staging, according to the 8th edition of the American Joint Committee

on Cancer (12); iii) no prior RT to the thorax; and iv) the presence of follow-up chest computed tomography (CT). The study was approved by the Korean National Institute for Bioethics Policy (approval no. P01-202207-01-025). Patient and tumor characteristics are given in Table I.

Simulation and treatment planning. All patients underwent CT simulation in the supine position and both arms were immobilized using a wing board. Free breathing was facilitated during the simulation and each treatment. In all cases, the prescribed dose to the ipsilateral whole breast was 40.05 Gy in 15 fractions of 2.67 Gy, 5 days per week for 3 weeks. The dose for tumor bed boost was 10 Gy in 4 fractions for clear resection margins and 12.5 Gy in 5 fractions for close or positive resection margins, using 2.5 Gy per fraction for 1 week. A total of 3 patients received electron-boost RT, while the remainder received boost RT using VMAT. None of the patients received regional nodal irradiation. The VMAT plan in the current study consisted of two partial arc beams that geometrically resembled the breast. The arrangement of the beams was optimized to lower the OAR doses while improving the planning target volume (PTV) coverage by resembling the breast shape using tangential arcs. The axillary nodal area was not included in the PTV. The VMAT treatment plans were produced by the Monaco RTP system (Elekta Instrument AB Stockholm) using an Elekta Versa HD treatment machine (Elekta Instrument AB Stockholm) with 5 mm multileaf collimators (MLC) for modeling. A total of two tangential photon arcs of 6 MV with arc lengths of 240˚, were applied to attain the prescribed dose (Fig. 1). The optimization plan produced by the Monaco RTP system provided >95% coverage of the target isodose and minimized the OAR tolerance dose. The dynamic MLC arc moved in the range of acute angles based on the angle of incidence of the lungs. Thus, the radiation dose to the ipsilateral lung was minimized. The dose for OAR was limited as follows: for the ipsilateral lung, V_5 (the percentage volume receiving 5 Gy) <0%, V_{10} (the percentage volume receiving 10 Gy) <35%, and V_{20} (the percentage volume receiving 20 Gy) <20%, mean heart dose <Gy and mean dose for contralateral breast <2 Gy.

Clinical and dosimetric analysis. Acute toxicities were defined during treatment and within 6 months post-RT. Regular follow-up visits and chest CTs were performed at 3 and 6 months post-RT. Lung and skin toxicities were graded using the Common Terminology Criteria for Adverse Events v.5.0 (13). The conformity index (CI) and homogeneity index (HI) were analyzed as follows: $CI=V_{RI}/TV$ (where V_{RI} and TV are the reference isodose volume and target volume, respectively), and $HI=I_{max}/RI$ (where I_{max} and RI are the maximum isodose in the target and reference isodoses, respectively) (14). The OAR dose and volume related to RP were analyzed using the Mann-Whitney U test and Fisher's exact test. Statistical analysis was performed using SPSS v.19 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Table I. Patient and tumor characteristics (n=23).

Characteristic	Value
Age, years[a]	50 (31-66)
Site, n (%)	
Right	8 (34.8)
Left	15 (65.2)
Pathological tumor stage , n (%)	
Tis	4 (17.4)
T1	14 (60.9)
T2	5 (21.7)
Pathological nodal stage, n (%)	
Yes	2 (8.7)
No	21 (91.3)
Neoadjuvant chemotherapy, n (%)	
Yes	2 (8.7)
No	21 (91.3)
Adjuvant chemotherapy, n (%)	
Yes	3 (13)
No	20 (87)
Hormone therapy, n (%)	
Yes	20 (87)
No	3 (13)
Resection margin, n (%)	
Negative	11 (47.8)
Close or positive	12 (52.2)
Ipsilateral whole breast target volume, cm^{3a}	418.07 (196.67-978.71)
Ipsilateral tumor bed target volume, cm^{3a}	79.66 (38.48-277.56)

[a]Median (range).

Results

Clinical analysis. Patient and tumor characteristics are summarized in Table I. None of the patients had underlying lung disease or a history of smoking. Among the 23 patients, eight had right-sided breast tumors and 15 had left-sided breast tumors. A total of 12 patients (52.2%) received 12.5 Gy in 5 fractions due to close or positive resection margins. Three patients received electron-boost RT; the remainder received boost RT using VMAT. The median follow-up duration was 10.1 months (range, 7.6-11.9). RP developed in seven patients (30.4%) at a median of 3.8 months (range, 2.3-4.2) post-treatment. None of these patients presented with RP-related symptoms; the diagnosis was based on radiologic findings observed on follow-up chest CT. Among the seven patients with RP, five had right-sided breast tumors, and two had left-sided breast tumors (71.4 vs. 28.6%, P=0.026). Grade 1 erythema was observed in 19 patients (82.6%), and four presented with grade 2 erythema (17.4%).

Dosimetric analysis. The RT characteristics are listed in Table II. In this study, the median ipsilateral whole breast target volume was 418.1 cm^3 (range, 196.7-978.7), and the median ipsilateral tumor bed target volume was 79.7 cm^3 (range, 38.5-277.6). In the univariate analysis (Table III), the

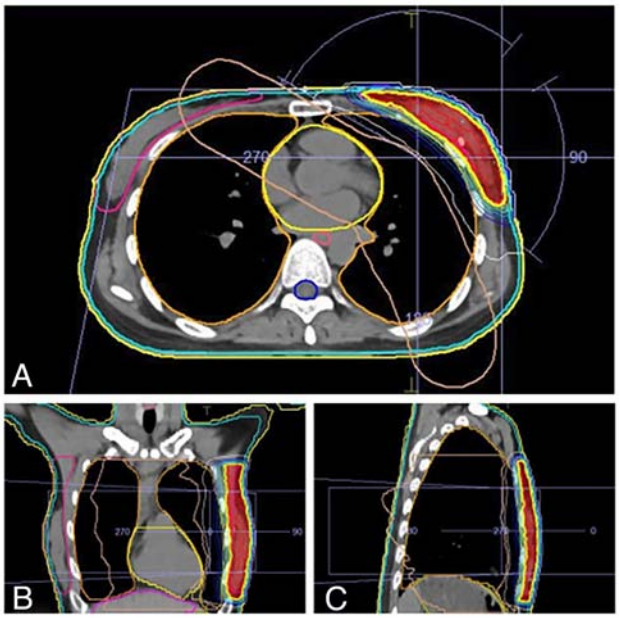

Figure 1. Image of isodose evaluation of left breast coverage by a hypofractionated volumetric modulated arc therapy plan: (A) axial image, (B) coronal image and (C) sagittal image.

mean target dose, $D_{105\%}$ (the dose received by 105% of the target volume), HI, mean lung dose, and ipsilateral lung V_{20} and V_{30} for ipsilateral whole breast RT were significantly associated with RP (P=0.039, 0.047, 0.018, 0.015, 0.018 and 0.003, respectively).

Discussion

The current study investigated the acute and subacute toxicities of HFX-VMAT in patients with EBC. It showed tolerable skin reactions of grade 2 or less and the occurrence of asymptomatic RP (30.4%). The present study identified a correlation of the following dosimetric factors with RP: Mean target dose, $D_{105\%}$, HI, mean lung dose and ipsilateral lung V_{20} and V_{30} for ipsilateral whole breast RT.

Traditionally, the radiation dose schedule for ipsilateral whole breast consisted of 45-50.4 Gy in fractions of 1.8-2 Gy over 5 weeks. In radiobiological terms, the α/β ratio is one of determinants of radiosensitivity, and breast cancer has a relatively low α/β ratio of 4 Gy (8). Therefore, breast cancer responds more sensitively to radiation therapy when the fraction size is larger than conventional fraction sizes. The START trial (7), a long-term follow-up HFX-RT study, showed the local control rate in breast cancer treatment with HFX-RT to be equivalent, with fewer or no differences in side effects to previous studies on conventional fractionation. Based on these studies (7,15,16), HFX-RT has been established as the standard treatment, with 40-40.5 Gy in 15-16 fractions for the ipsilateral whole breast (17). In 2018, the American Society for Radiation Oncology (ASTRO) (18) recommended an HFX regimen of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions. The biologically effective doses in these regimens (17,18), computed by the linear-quadratic model and using α/β=4 for breast cancer, were equivalent to 44.8-48.9 Gy in fractions of 1.8 Gy.

Table II. Radiotherapy characteristics (n=23).

A, Ipsilateral whole breast target

Characteristic	Median (range)
Mean target dose, Gy	40.19 (39.35-40.91)
$D_{95\%}$, %	95.69 (95.01-98.31)
$D_{105\%}$, %	5 (0-5)
CI	0.96 (0.95-0.98)
HI	1.15 (1.10-1.18)
Mean lung dose, Gy	6.68 (4.08-8.56)
Lung $V_{5\ Gy}$, %	38.18 (22.44-49.98)
Lung $V_{10\ Gy}$, %	20.14 (12.56-33.14)
Lung $V_{20\ Gy}$, %	7.32 (3.01-13.31)
Lung $V_{30\ Gy}$, %	1.24 (0.03-5.03)
Mean heart dose, Gy	0.47 (0.05-1.12)
Heart D_{max}, Gy	1.93 (0.28-4.19)

B, Ipsilateral tumor bed target

Characteristic	Median (range)
Mean target dose, Gy	12.32 (9.85-13.12)
$D_{95\%}$, %	96.08 (92.56-99.65)
$D_{105\%}$, %	0 (0-99.27)
$D_{110\%}$, %	0 (0-98.19)
CI	0.96 (0.93–1.00)
HI	1.16 (1.09–1.53)
Mean lung dose, Gy	1.01 (0.11-1.88)
Lung $V_{5\ Gy}$, %	1.34 (0-5.33)
Lung $V_{10\ Gy}$, %	0 (0-0.05)
Mean heart dose, Gy	0.47 (0.05-1.12)
Heart D_{max}, Gy	1.93 (0.28-4.19)

$D_{95\%}$, dose received by 95% of the target volume; $D_{105\%}$, dose received by 105% of the target volume; CI, conformity index; HI, homogeneity index; $V_{5\ Gy}$, percentage volume receiving 5 Gy; $V_{10\ Gy}$, percentage volume receiving 10 Gy; $V_{20\ Gy}$, percentage volume receiving 20 Gy; $V_{30\ Gy}$, percentage volume receiving 30 Gy; D_{max}, maximum dose; $D_{110\%}$, dose received by 110% of the target volume.

RP, an acute inflammatory reaction with exudation in the alveolar space, develops within 4-12 weeks of breast RT and can result in changes in radiologic findings or lung function (19-23). Symptomatic RP includes dry cough, dyspnea, chest discomfort, or mild fever. A number of studies have reported a relationship between the risk of RP and dosimetric parameters, including total radiation dose, fractionation, mean lung dose and irradiated lung volume, such as V_5, V_{10}, V_{20}, and V_{30} (22,24,25). Advanced techniques, such as IMRT, VMAT and helical tomotherapy, can improve dosimetry and reduce acute toxicities through the RT planning process (26,27); thus, they are also useful in HFX-RT. In the present study, irradiated lung volume was restricted to reduce the risk of RP. The radiation dose constraints for the ipsilateral lung in the current study fall within the ranges of lung cancer RT guidelines (28).

Table III. Univariate analysis of factors for radiation pneumonitis and dosimetry.

	Radiation pneumonitis		
	No	Yes	
Variable	Mean (SD)	Mean (SD)	P-value
Ipsilateral whole breast target			
Volume	443.04 (219.44)	421.96 (151.66)	0.871
Mean target dose, Gy	40.24 (0.31)	40.00 (0.36)	0.039
$D_{95\%,}$ %	95.97 (0.95)	95.55 (0.63)	0.154
$D_{105\%,}$ %	3.26 (2.22)	2.18 (2.64)	0.047
CI	0.96 (0.01)	0.96 (0.01)	0.871
HI	1.15 (0.01)	1.13 (0.02)	0.018
Mean lung dose, Gy	6.35 (1.11)	7.14 (0.72)	0.015
Ipsilateral lung V5 Gy, %	36.63 (8.40)	39.23 (3.27)	0.974
Ipsilateral lung V10 Gy, %	20.08 (5.28)	21.94 (2.99)	0.118
Ipsilateral lung V20 Gy,%	7.47 (2.42)	9.60 (3.70)	0.018
Ipsilateral lung V30 Gy, %	1.34 (1.24)	3.27 (2.16)	0.003
Ipsilateral tumor bed target			
Volume			
Mean target dose (Gy)	11.29 (1.32)	12.00 (1.36)	0.018
$D_{95\%}$ (%)	96.14 (2.04)	96.41 (1.55)	0.341
$D_{105\%}$ (%)	5.21 (15.19)	14.91 (37.22)	0.222
$D_{110\%}$ (%)	0.88 (3.44)	14.03 (37.11)	0.922
CI	0.96 (0.02)	0.97 (0.01)	0.341
HI	1.14 (0.05)	1.21 (0.14)	0.198
Mean lung dose, Gy	1.04 (0.47)	0.83 (0.50)	0.922
Ipsilateral lung $V_{5\ Gy}$, %	1.85 (1.73)	1.65 (1.55)	0.123
Ipsilateral lung $V_{10\ Gy}$,%	0.00 (0.01)	0.01 (0.02)	0.118

$D_{95\%,}$ dose received by 95% of the target volume; $D_{105\%,}$ dose received by 105% of the target volume; CI, conformity index; HI, homogeneity index; $V_{5\ Gy}$, percentage volume receiving 5 Gy; $V_{10\ Gy}$, percentage volume receiving 10 Gy; $V_{20\ Gy,}$ percentage volume receiving 20 Gy; $V_{30\ Gy}$, percentage volume receiving 30 Gy; $D_{110\%,}$ dose received by 110% of the target volume.

Several studies have also tried to control the OAR dose, especially to prevent RP (27-30) and showed an OAR dose constraint range comparable to that of the current study.

Based on published data (26-32), the current study applied the valid lung dosing constraints to plan HFX-VMAT. For OAR, the doses were limited as follows: For ipsilateral lung, V_5 <50%, V_{10} <35% and V_{20} <20%; mean heart dose <3 Gy; and mean contralateral breast dose <2 Gy. It is widely reported that limiting dosimetric parameters, such as V_{20} or V_{30}, contributes to reducing the risk of RP (27,29). In the VMAT study with simultaneous integrated boost (32), which prescribed 40.5 and 48 Gy in 15 fractions to the ipsilateral whole breast and tumor bed boost, respectively, certain dose limits were established. The mean dose limits were defined as <10 Gy and V20 <10% for the ipsilateral lung, while the mean heart dose was limited to <4 Gy. When planning RT, the current study restricted V_5 of the ipsilateral lung with a median value of 38.18%, which provided evidence that a low radiation dose induces RP (30,33). McKenzie *et al* (34) prescribed 42.56 Gy in 16 fractions and set lung constraints at 30-35% for $V_{17.5}$, which, in HFX regimens, is radiobiologically equivalent to V_{20} in conventional regimens. Following their HFX regimen, they reported a range of 24-36% of $V_{17.5}$ and two cases of RP. In 2018, ASTRO recommended that, in HFX regimens, the V_{16} of the ipsilateral lungs be limited to 15-20% (18). In the current study, the V_{20} of the ipsilateral lungs ranged from 3.01 to 13.31%, falling within the ASTRO guidelines.

The primary limitations of the current study are the small sample size and the focus on acute/subacute toxicity. The factors that caused radiation pneumonitis included interstitial lung disease, chronic obstructive pulmonary disease and diabetes mellitus. The present study included only two cases with histories of diabetes, due to its small sample size, and thus there was no statistically significant analysis of diabetes and radiation pneumonitis. Therefore, it is necessary to conduct a follow-up study with a larger sample size. The present study also showed that RP did not occur in the group with a high mean dose of breast target. It is hypothesized that the inclination of clinicians to prioritize lung dose reduction is reflected in the selection of RT plans to satisfy the condition

of target isodose coverage of more than 95%. During the RT planning stage, the current study conducted a comparison of multiple RT plans. Among these plans, it selected one that achieved a target isodose coverage of over 95% while further reducing the lung dose. However, rather than focusing just on the tumor, it chose a plan with a relatively lower mean lung dose. In the process of lowering the mean lung dose, the lung constraint was given more weight, resulting in higher mean and maximum target dose.

However, the strengths of the current study are that it was conducted at a single institution and focused on a single radiation technique, HFX-VMAT. The VMAT technique is widely used to treat various cancers, and the HFX-RT schedule has been applied to breast cancer treatment (35,36). Thus, the focus of the current study on HFX-VMAT is novel and provides convincing data for the literature. The data on long-term follow-up after HFX-RT in EBC is lacking, especially for IMRT, including VMAT, despite reports of late toxicity, such as fibrosis and secondary malignancy (7,26,27,32,37). Further research would be helpful in identifying the long-term treatment outcomes after HFX-RT in EBC.

In conclusion, the current study demonstrated tolerable acute and subacute toxicities following HFX-VMAT and the correlation between its dosimetric parameters with RP in EBC patients. It suggested that HFX-VMAT can be an effective and safe treatment option for EBC and that RT planning must be considered to reduce the incidence of RP. However, a longer follow-up is necessary to determine the long-term outcomes following HFX-RT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

MC and JL confirm the authenticity of all the raw data. MC and JL designed the study and performed the analysis and interpretation of data. JL drafted the manuscript. MC conceived the review and revised the manuscript. Both authors have read and approved the manuscript.

Ethics approval and consent to participate

The study was approved by the Korean National Institute for Bioethics Policy (approval no. P01-202207-01-025).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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