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Dosimetric comparison of the heart substructures with IMRT and VMAT techniques in left breast radiotherapy: The effect of deep inspiratory breath-hold

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ABSTRACT

Background: This study aimed to compare the doses received by the four chambers and vascular structures of the heart during adjuvant radiotherapy (RT) after left breast -conserving surgery (BCS) using intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT) techniques. ***Material and Methods***: Simulation images were taken of 14 patients who underwent left BCS with both free-breathing (FB) and deep inspiration breath-hold (DIBH) techniques. Left breast RT was planned with both IMRT and VMAT. Planned target volumes 50 and 60, homogeneity index, conformity index, and monitor unit values, as well as radiation doses received by organs at risk, were compared. ***Results***: In IMRT compared to VMAT, in the heart (D_{mean}, V_{10}, V_2) and heart substructures (left ventricle [V_5] , right ventricle [D_{mean}], right atrium [D_{mean}, D_{max}], left atrium [D_{mean}, V_5], right coronary artery [RCA; D_{mean}, D_{max}], left artery coronary main [LACM; D_{mean}], and left circumflex artery [LCxA; D_{mean}, D_{max}]), significant dose reductions were observed. When FB and DIBH results were compared, in the DIBH technique, the heart (D_{mean}, V_{25}, V_{10}, V_2) and heart substructures (left ventricle [D_{mean}, D_{max}, V_{23}, V_5], right ventricle [D_{mean}, D_{max}], right atrium [D_{mean}, D_{max}], left atrium [D_{mean}, D_{max}], left anterior descending artery [D_{mean}, D_{max}, V_{20}], RCA [D_{max}], LACM [D_{mean}], and LCxA [D_{mean}, D_{max}]), doses were significantly decreased. ***Conclusion***: In RT of patients with left BCS, significant dose reductions occurred in the lung, heart, and almost all substructures of the heart using DIBH compared to FB.

INTRODUCTION

Adjuvant radiotherapy (RT) in breast cancer carries long-term cardiac risks. In particular, conventional planning techniques and large irradiation areas increase this risk [(1)]. The relative risk of cardiac mortality is estimated to increase by 0.04 per Gy of radiation to the heart [(2)]. Two hypotheses regarding RT-induced cardiovascular damage have been proposed. The first hypothesis stated that radiation increases the frequency of myocardial infarction by interacting with one or more steps of the pathogenic pathway of age-related coronary artery atherosclerosis. The second hypothesis proposed that the lethality of myocardial infarction increases due to pathologies unrelated to radiation [(3)]. It has been stated that cardiac risk increases, particularly in the first 5 years after treatment, and continues for 20 years [(4)].

Cardiac risk can be minimized by reducing the doses taken by the heart and the heart's substructures during breast RT. It has been shown that contouring the heart's substructures as organs at risk (OARs) can reduce the dose to these structures without compromising the dose distribution, even in conventional and free-breathing (FB) techniques [(5)]. In addition, dose reduction in OARs has become more pronounced with the introduction of advanced technologies such as intensity-modulated RT (IMRT), volumetric-modulated arc therapy (VMAT), deep inspiration breath-hold (DIBH), and proton therapy [(6-8)]. Breast RT with the DIBH technique was first described in a study published in 2001, and significant reductions in the radiation doses received by the heart were shown with this technique [(9)]. In the following years, breast RT with DIBH has attracted significant interest, and many studies have been published on its efficacy and dose-reduction capacity [(10-14)]. In ongoing studies, the effects of the DIBH technique, together with different planning modalities, on the ipsilateral lung, total lung, heart, left ventricle and left anterior descending artery (LAD) are being investigated.

In our study, we examined the effects of RT plans on the other 3 chambers of the heart, right coronary artery (RCA), left artery coronary main (LACM), and

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left circumflex artery (LCxA), in addition to other known OARs. We aimed to compare the doses received by OARs during FB and DIBH techniques employed during IMRT and VMAT plans.

MATERIALS AND METHODS

Patient selection and planning

Between January 2020 and June 2021, 14 patients who underwent left breast-conserving surgery (BCS) and were referred for RT in our clinic were included in the study. Two simulation images with 3 mm sections were taken of the patients, using both FB and DIBH techniques. The Philips Brilliance Big Bore Computed Tomography Simulator was used to take the images and the RPM Respiratory Gating System (version 1.7.5; Varian Medical Systems) was used for respiratory monitoring. OARs were contoured on the images under the guidance of a radiologist with reference to the Radiation Therapy Oncology Group guidelines and heart atlas study by Feng *et al.* (15). While the left breast was contoured and a dose of 50 Gy was defined, a dose of 60 Gy was defined for the tumor bed by contouring, with the support of a general surgeon, the lumpectomy tumor site, clips, and seroma; 95% of the target volumes (D95%) were intended to receive treatment doses of 50 and 60 Gy with a 95%–107% dose homogeneity. The simultaneous integrated boost technique and 6 MV X-rays in 28 fractions (178.5 cGy/day for the left breast, 214 cGy/day for the tumor bed) were preferred for dose administration. Plans with 7–9 fields in FB and 5–7 fields in DIBH were made for IMRT, while plans with 4 half arcs were made in FB and DIBH for VMAT. All plans were made using the Eclipse Treatment Planning System (version 15.1; Varian Medical Systems). The Varian Clinac IX was used as the RT treatment device. The radiation dose received by the planned target volume (PTV) 50 and 60, homogeneity index (HI), conformity index (CI), monitor unit (MU), and OARs (both lungs, right breast, esophagus, spinal cord, whole heart, and substructures of the heart) were compared for the 4 plans made for each patient. Dose distributions and dose-volume histograms of the same patient in 4 different techniques are shown in figures 1 and 2, respectively.

Statistical analysis

The conformity of the data to the normal distribution was evaluated by histogram, Q-Q plots, and the Shapiro–Wilk test. Homogeneity of variance was tested with Levene's test. The paired *t*-test was applied for quantitative measurements with 2 replicates. Data were evaluated with R 4.0.0 software (www.r-project.org). The significance level was accepted as $p < 0.05$.

Power analysis

A power analysis is performed to identify the necessary sample size. For $\alpha = 0.05$, power = 0.85, and effect size = 0.788, the minimum sample size was 14. Power analyses were conducted using GPower 3.1.9.7 software.

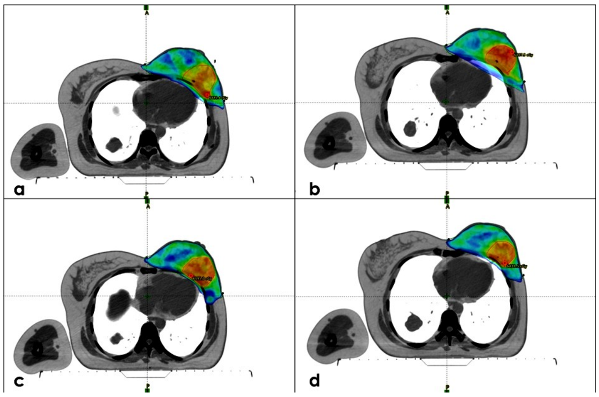

Figure 1. Dose distribution image for patient X. 95% of the target volumes (D95%) were intended to receive a 50 and 60 Gy treatment dose, with a dose homogeneity of 95–107%. **a** IMRT-FB Intensity-modulated radiotherapy-Free breath, **b** IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, **c** VMAT-FB Volumetric-modulated arc therapy-Free breath, **d** VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

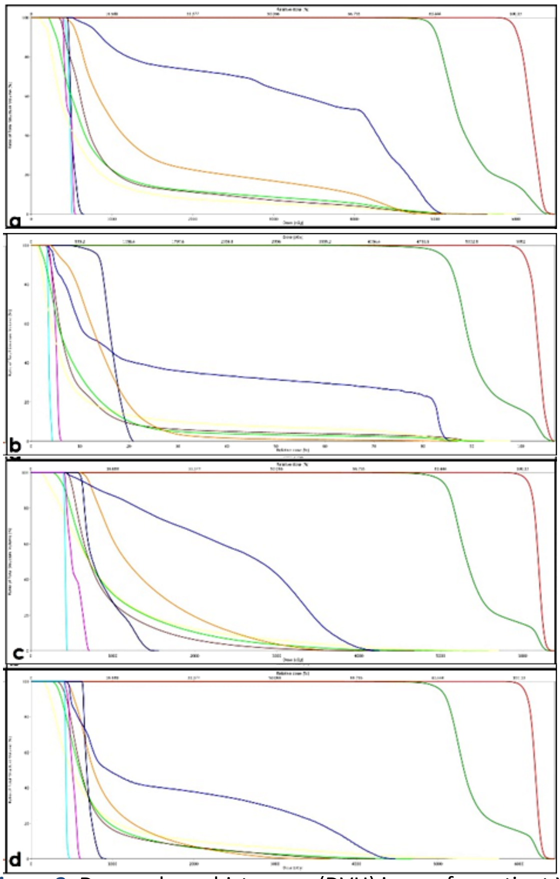

Figure 2. Dose-volume histogram (DVH) image for patient X. The colored curves in DVH represent: Dark green PTV 50, Red PTV 60, Pink Heart, Brown Left ventricle, Orange Right ventricle, Blue LAD, Dark blue RCA, Cyan LACM, Magenta LCxA, and Yellow Left lung. PTV Planning target volume, LAD Left anterior descending artery, RCA Right coronary artery, LACM Left artery coronary main, LCxA Left circumflex artery. **a** IMRT-FB Intensity-modulated radiotherapy-Free breath, **b** IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, **c** VMAT-FB Volumetric-modulated arc therapy-Free breath, **d** VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

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RESULTS

Table 1 compares PTV, HI, CI, and MU values for the 4 planning techniques. Table 2 shows the doses received by the OARs during IMRT and VMAT. Table 3 presents the doses received by the OARs when the FB and DIBH techniques were employed.

Table 1. Comparison of PTV, HI, CI, and MU values.

Parameters		IMRT FB	IMRT DIBH	*p*	VMAT FB	VMAT DIBH	*p*
PTV 60	D%2(Gy)	63.68±0.66	63.66±0.64	0.902	63.21±0.60	63.20±0.45	0.945
	D%98(Gy)	59.79±0.44	59.62±0.54	0.335	59.73±0.44	59.84±0.31	0.126
	D%50(Gy)	61.93±0.40	62.03±0.32	0.315	61.96±0.36	61.92±0.28	0.679
PTV 50	D%98(Gy)	49.35±1.05	49.15±0.64	0.498	48.59±0.50	48.61±0.54	0.827
	D%50(Gy)	52.94±0.53	53.16±0.43	0.059	52.81±0.49	52.80±0.68	0.922
HI		0.06±0.01	0.06±0.02	0.876	0.05±0.01	0.05±0.01	0.435
CI		1.19±0.08	1.21±0.07	0.129	1.11±0.03	1.11±0.05	0.870
MU		1827.79±462.62	1487.64±425.59	**<0.001**	532.36±42.47	521.93±41.62	0.279

Values are expressed as mean±SD. The bold value indicates statistical significance (p <0.05). IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric -modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold, PTV Planning target volume, HI Homogeneity index, (ICRU 83/HI of zero is ideal); (D2%-D98%) /D50%, CI Conformity index, (ICRU 62/CI of 1.0 is ideal); Volume of PTV covered by the 95% isodose curve/volume of PTV, MU monitor unit.

Table 2. Comparison of OAR doses at IMRT and VMAT.

Parameters		IMRT FB	VMAT FB	*p*	IMRT DIBH	VMAT DIBH	*p*
Heart	D_{mean} (Gy)	8.59±1.78	9.33±1.59	**0.049**	5.74±1.58	7.27±1.51	0.362
	V_{25} (%)	5.56±3.26	4.15±2.62	**0.006**	2.16±2.06	1.33±1.68	**0.017**
	V_{10} (%)	22.00±10.16	28.80±9.81	**0.040**	11.53±8.24	17.29±8.56	**<0.001**
	V_{2} (%)	98.83±3.43	99.89±0.40	**<0.001**	89.79±10.03	98.68±4.31	**0.002**
Ipsilatarel Lung	D_{mean} (Gy)	12.72±2.32	13.25±1.42	**0.018**	12.03±2.25	12.79±1.94	**0.035**
	V_{20} (%)	18.25±4.70	18.99±2.87	0.414	17.57±4.60	18.81±4.17	0.085
	V_{12} (%)	32.30±9.99	35.38±6.09	0.191	28.92±7.35	34.31±7.65	**0.001**
	V_{5} (%)	69.87±17.50	85.41±10.40	**<0.001**	61.19±14.53	79.15±13.07	**<0.001**
Esophagus	D_{mean} (Gy)	5.22±4.37	6.82±3.55	**0.002**	4.59±3.80	6.36±3.28	**0.001**
Spinal Cord	D_{max} (Gy)	11.09±10.54	9.92±7.30	0.325	7.87±8.62	9.16±7.92	0.079
LAD	D_{mean} (Gy)	17.90±8.47	15.27±7.85	**0.004**	11.40±5.51	10.98±3.80	0.603
	D_{max} (Gy)	38.50±13.76	32.65±11.72	**0.004**	31.67±16.68	25.17±11.66	**0.011**
	V_{40} (%)	14.51±18.92	4.21±9.99	**0.047**	4.67±8.73	0.56±2.11	0.053
	V_{20} (%)	24.22±22.92	28.96±27.18	0.370	14.14±17.39	11.46±14.22	0.317
Left Ventricle	D_{mean} (Gy)	10.90±3.74	9.31±2.73	**0.001**	6.72±2.56	7.10±2.74	0.394
	D_{max} (Gy)	45.47±12.42	40.08±11.14	**0.018**	34.67±14.93	29.65±13.00	0.063
	V_{23} (%)	10.33±8.73	5.94±6.57	**0.005**	3.48±3.93	1.42±2.09	**0.025**
	V_{5} (%)	84.06±19.60	84.26±16.97	0.951	49.68±30.80	62.31±25.42	**0.023**
Left Atrium	D_{mean} (Gy)	3.75±0.91	4.56±0.95	**0.021**	3.04±1.28	4.59±1.06	**0.001**
	D_{max} (Gy)	7.37±2.18	7.00±1.78	0.601	5.83±2.23	7.59±2.95	0.079
	V_{5} (%)	16.00±21.86	32.23±34.72	0.154	9.02±17.80	27.16±30.32	**0.049**
Right Ventricle	D_{mean} (Gy)	9.95±2.92	11.15±2.45	0.091	6.74±3.03	8.20±3.19	**0.001**
	D_{max} (Gy)	43.34±10.16	35.70±8.56	**<0.001**	30.33±14.74	25.40±9.26	**<0.001**
Right Atrium	D_{mean} (Gy)	3.77±1.03	6.67±2.25	**<0.001**	2.83±0.98	5.10±1.88	**0.001**
	D_{max} (Gy)	8.93±4.73	15.41±6.53	**0.001**	6.41±3.57	11.50±4.34	**<0.001**
Right Breast	D_{mean} (Gy)	3.29±0.82	5.85±0.95	**<0.001**	2.58±0.87	5.92±1.04	**<0.001**
Right Lung	D_{mean} (Gy)	4.60±2.43	7.07±1.58	**<0.001**	3.56±1.52	6.54±0.79	**<0.001**
	V_{5} (%)	28.04±19.01	60.62±15.48	**<0.001**	19.65±14.83	53.84±10.27	**<0.001**
Total Lung	D_{mean} (Gy)	8.28±2.14	9.84±1.34	**0.001**	7.46±1.60	9.37±1.14	**<0.001**
	V_{20} (%)	9.31±3.85	9.78±2.14	0.421	8.63±2.65	9.65±2.07	**0.018**
RCA	D_{mean} (Gy)	6.67±2.63	11.30±3.85	**<0.001**	4.93±1.87	9.28±3.16	**0.002**
	D_{max} (Gy)	8.51±3.45	15.20±4.97	**<0.001**	6.59±2.56	12.00±3.82	**0.002**
LACM	D_{mean} (Gy)	5.27±1.51	5.34±1.02	**0.005**	4.32±2.18	5.73±1.24	**0.026**
	D_{max} (Gy)	6.02±1.93	5.87±1.36	0.793	4.84±2.45	6.12±1.29	0.057
LCxA	D_{mean} (Gy)	5.97±1.69	5.51±0.92	0.383	4.48±1.48	5.68±1.10	**0.004**
	D_{max} (Gy)	7.28±2.33	6.56±1.27	0.322	5.63±2.15	6.75±1.34	**0.036**

Values are expressed as mean±SD. The bold value indicates statistical significance (p <0.05). IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric -modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold, Dmean mean dose, Dmax maximum dose, VX (%) The percent volume of organ receiving X Gy dose, LAD Left anterior descending artery, RCA Right coronary artery, LACM Left artery coronary main, LCxA Left circumflex artery.

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Table 3. Comparison of OAR doses at FB and DIBH.

Parameters		IMRT FB	IMRT DIBH	p	VMAT FB	VMAT DIBH	p
Heart	D_{mean} (Gy)	8.59±1.78	5.74±1.58	0.390	9.33±1.59	7.27±1.51	**<0.001**
	V_{25} (%)	5.56±3.26	2.16±2.06	**<0.001**	4.15±2.62	1.33±1.68	**<0.001**
	V_{10} (%)	22.00±10.16	11.53±8.24	**<0.001**	28.80±9.81	17.29±8.56	**<0.001**
	V_2 (%)	98.83±3.43	89.79±10.03	**<0.001**	99.89±0.40	98.68±4.31	0.266
Ipsilatarel Lung	D_{mean} (Gy)	12.72±2.32	12.03±2.25	**0.018**	13.25±1.42	12.79±1.94	0.192
	V_{20} (%)	18.25±4.70	17.57±4.60	0.221	18.99±2.87	18.81±4.17	0.817
	V_{12} (%)	32.30±9.99	28.92±7.35	**0.038**	35.38±6.09	34.31±7.65	0.527
	V_5 (%)	69.87±17.50	61.19±14.53	**0.023**	85.41±10.40	79.15±13.07	**0.014**
Esophagus	D_{mean} (Gy)	5.22±4.37	4.59±3.80	0.262	6.82±3.55	6.36±3.28	0.356
Spinal Cord	D_{max} (Gy)	11.09±10.54	7.87±8.62	**0.034**	9.92±7.30	9.16±7.92	0.193
LAD	D_{mean} (Gy)	17.90±8.47	11.40±5.51	**0.001**	15.27±7.85	10.98±3.80	**0.021**
	D_{max} (Gy)	38.50±13.76	31.67±16.68	0.081	32.65±11.72	25.17±11.66	**0.011**
	V_{40} (%)	14.51±18.91	4.67±8.73	0.058	4.21±9.99	0.56±2.11	0.211
	V_{20} (%)	24.22±22.92	14.14±17.39	0.076	28.96±27.18	11.46±14.22	**0.006**
Left Ventricle	D_{mean} (Gy)	10.90±3.74	6.72±2.56	**<0.001**	9.31±2.72	7.10±2.74	**0.001**
	D_{max} (Gy)	45.47±12.42	34.67±14.93	**0.002**	40.08±11.14	29.65±13.00	**<0.001**
	V_{23} (%)	10.33±8.73	3.48±3.93	**0.006**	5.94±6.57	1.42±2.09	**0.009**
	V_5 (%)	84.06±19.60	49.68±30.80	**<0.001**	84.26±16.97	62.31±25.42	**<0.001**
Left Atrium	D_{mean} (Gy)	3.75±0.91	3.04±1.28	**0.037**	4.56±0.95	4.59±1.06	0.912
	D_{max} (Gy)	7.37±2.18	5.83±2.23	**0.002**	7.00±1.78	7.59±2.95	0.471
	V_5 (%)	16.00±21.86	9.02±17.80	0.229	32.23±34.72	27.16±30.32	0.548
Right Ventricle	D_{mean} (Gy)	9.95±2.92	6.74±3.03	**0.001**	11.15±2.45	8.20±3.19	**0.001**
	D_{max} (Gy)	43.34±10.16	30.33±14.74	**0.001**	35.70±8.56	25.40±9.26	**<0.001**
Right Atrium	D_{mean} (Gy)	3.77±1.03	2.83±0.98	**0.004**	6.67±2.25	5.10±1.88	**0.014**
	D_{max} (Gy)	8.93±4.73	6.41±3.57	**0.013**	15.41±6.53	11.50±4.34	**0.032**
Right Breast	D_{mean} (Gy)	3.29±0.82	2.58±0.87	**0.007**	5.85±0.95	5.92±1.04	0.653
Right Lung	D_{mean} (Gy)	4.60±2.43	3.56±1.52	0.181	7.07±1.58	6.54±0.79	0.176
	V_5 (%)	28.04±19.01	19.65±14.83	0.190	60.62±15.48	53.84±10.27	**0.027**
Total Lung	D_{mean} (Gy)	8.28±2.14	7.46±1.60	0.067	9.84±1.34	9.37±1.14	0.117
	V_{20} (%)	9.31±3.85	8.63±2.65	0.420	9.78±2.14	9.65±2.07	0.771
RCA	D_{mean} (Gy)	6.67±2.63	4.93±1.87	0.063	11.30±3.85	9.28±3.16	0.062
	D_{max} (Gy)	8.51±3.45	6.59±2.56	0.134	15.20±4.97	12.00±3.82	**0.031**
LACM	D_{mean} (Gy)	5.27±1.51	4.32±2.18	**0.002**	5.34±1.02	5.73±1.24	0.298
	D_{max} (Gy)	6.02±1.93	4.84±2.45	0.109	5.87±1.36	6.12±1.29	0.578
LCxA	D_{mean} (Gy)	5.97±1.69	4.48±1.48	**<0.001**	5.51±0.92	5.68±1.10	0.673
	D_{max} (Gy)	7.28±2.33	5.63±2.15	**0.001**	6.56±1.27	6.75±1.34	0.700

Values are expressed as mean±SD. The bold value indicates statistical significance (p <0.05). IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric -modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold, Dmean mean dose, Dmax maximum dose, VX (%) The percent volume of organ receiving X Gy dose, LAD Left anterior descending artery, RCA Right coronary artery, LACM Left artery coronary main, LCxA Left circumflex artery.

PTV coverage, HI, CI, and MU

There was no difference between the VMAT and IMRT plans in PTV 60 D2% (near-maximum dose), D98% (near-minimum dose), and D50% (mean dose) values or PTV 50 D98% and D50% values. There was no significant difference between VMAT and IMRT in HI and CI values, though the MU value was significantly lower in IMRT-DIBH compared to IMRT-FB (p < 0.001; table 1).

Heart dose

The lowest D_{mean} dose to the heart, 5.74 Gy, occurred with the IMRT-DIBH plan, while the highest, 9.33 Gy, occurred with the VMAT-FB plan. The V_{25} volume was lowest, at 1.33%, with the VMAT-DIBH plan and highest, at 5.56%, with the IMRT-FB plan. V_{10} volume was lowest with IMRT-DIBH (11.53%) and highest with VMAT-FB (28.80%), and V_2 volume was lowest with IMRT-DIBH (89.79%) and highest with VMAT-FB (99.89%; figure 3, tables 2 and 3).

Heart substructure dose

Left ventricle: The lowest D_{mean} dose to the left ventricle, 6.72 Gy, occurred with the IMRT-DIBH plan, and the highest, 10.90 Gy, occurred with the IMRT-FB plan. The lowest D_{max} dose occurred with VMAT-DIBH (29.65 Gy), while the highest occurred with IMRT-FB (45.47 Gy). V_{23} volume was lowest with VMAT-DIBH (1.42%) and highest with IMRT-FB (10.33%). The lowest V_5 volume was seen with IMRT-DIBH (49.68%) and the highest was seen with VMAT-FB (84.26%; figure 4, tables 2 and 3).

Right ventricle: The lowest D_{mean} dose to the right ventricle, 6.74 Gy, occurred with the IMRT-DIBH plan, while the highest, 11.15 Gy, occurred with the VMAT-FB plan. The lowest D_{max} dose occurred with VMAT-DIBH (25.40 Gy) and the highest occurred with IMRT-FB (43.34 Gy; tables 2 and 3).

Left atrium: The lowest D_{mean} dose to the left atrium, 3.04 Gy, was provided by the IMRT-DIBH plan, and the highest, 4.59 Gy, was provided by the VMAT-DIBH plan. The lowest D_{max} dose was 5.83 Gy and occurred with the IMRT-DIBH plan, while the highest was 7.59 Gy and occurred with the VMAT-DIBH plan. The lowest V_5 volume was seen with the IMRT-DIBH plan

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(9.02%) and the highest was seen with the VMAT-FB plan (32.32%; tables 2 and 3).

Right atrium: The lowest D_{mean} dose to the right atrium was 2.83 Gy and occurred with the IMRT-DIBH plan, while the highest was 6.67 Gy and occurred with the VMAT-FB plan. The lowest D_{max} dose, 6.41 Gy, was provided by the IMRT-DIBH plan, while the highest, 15.41 Gy, was provided by the VMAT-FB plan (tables 2 and 3).

LAD: The lowest D_{mean} dose to the LAD, 10.98 Gy, occurred with the VMAT-DIBH plan, and the highest, 17.90 Gy, occurred with the IMRT-FB plan. The lowest D_{max} dose of 25.17 Gy occurred with VMAT-DIBH, while the highest D_{max} dose of 38.50 Gy occurred with IMRT-FB. V_{40} volume was lowest with VMAT-DIBH (0.56%) and highest with IMRT-FB (14.51%), and V_{20} volume was lowest with VMAT-DIBH (11.46%) and highest with VMAT-FB (28.96%; figure 5, tables 2 and 3).

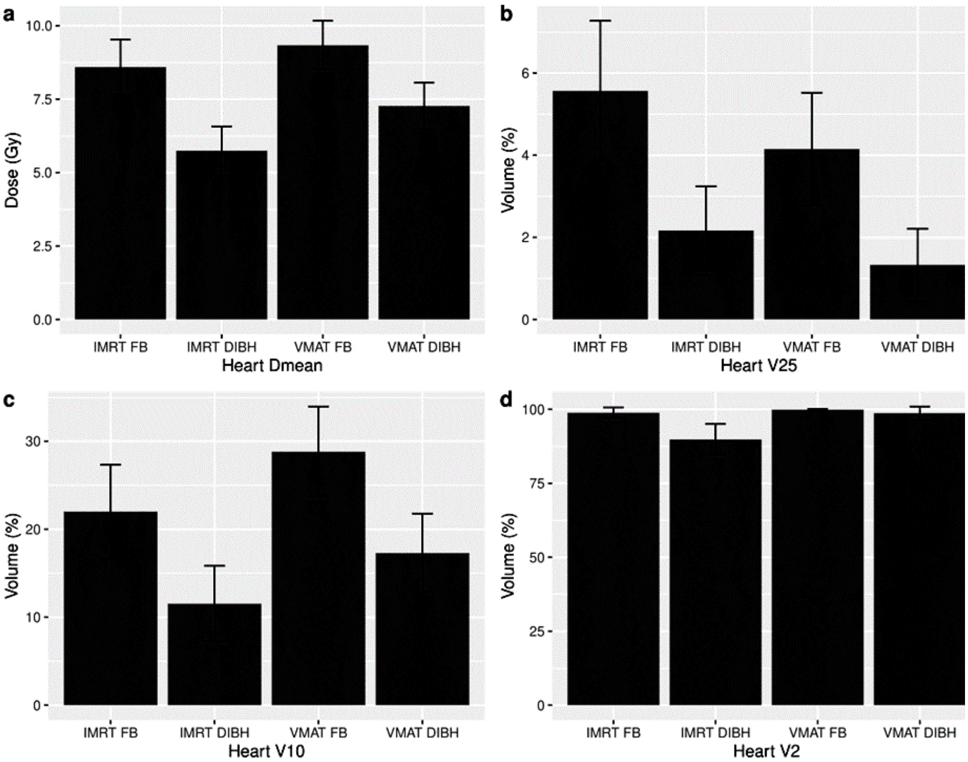

Figure 3. Mean±1.96*Standard error. Graphical view of heart Dmean **(a)**, V25 **(b)**, V10 **(c)** and V2 **(d)** values in four different planning techniques. Dmean mean dose, VX (%) The percent volume of organ receiving X Gy dose IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric-modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

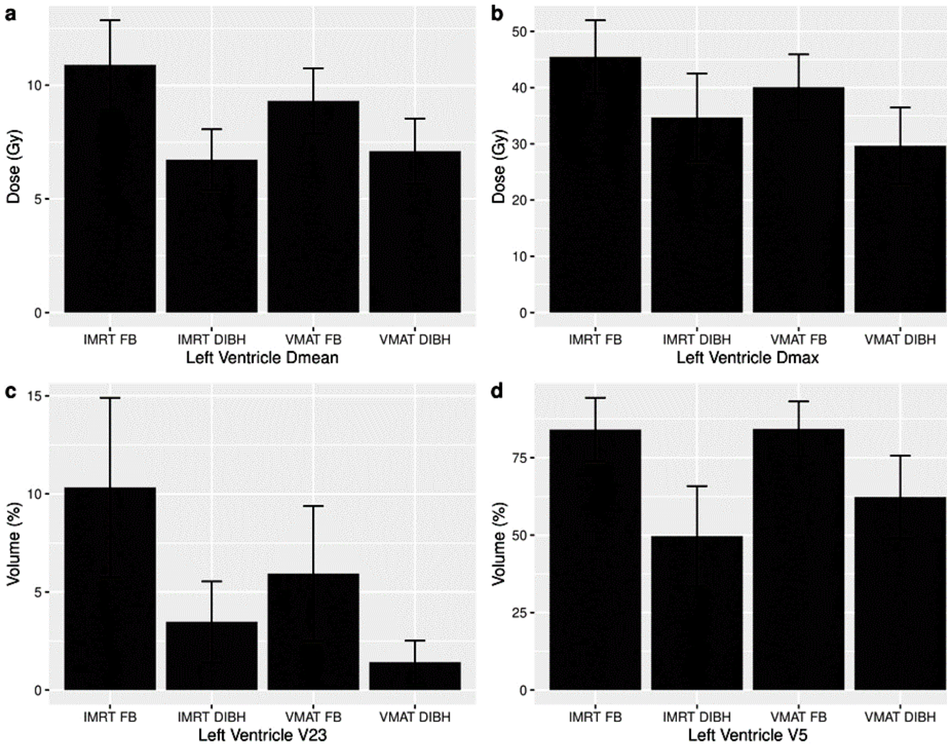

Figure 4. Mean±1.96*Standard error. Graphical view of left ventricle Dmean **(a)**, Dmax **(b)**, V23 **(c)** and V5 **(d)** values in four different planning techniques. Dmean mean dose, Dmax maximum dose, VX (%) The percent volume of organ receiving X Gy dose, IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric-modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

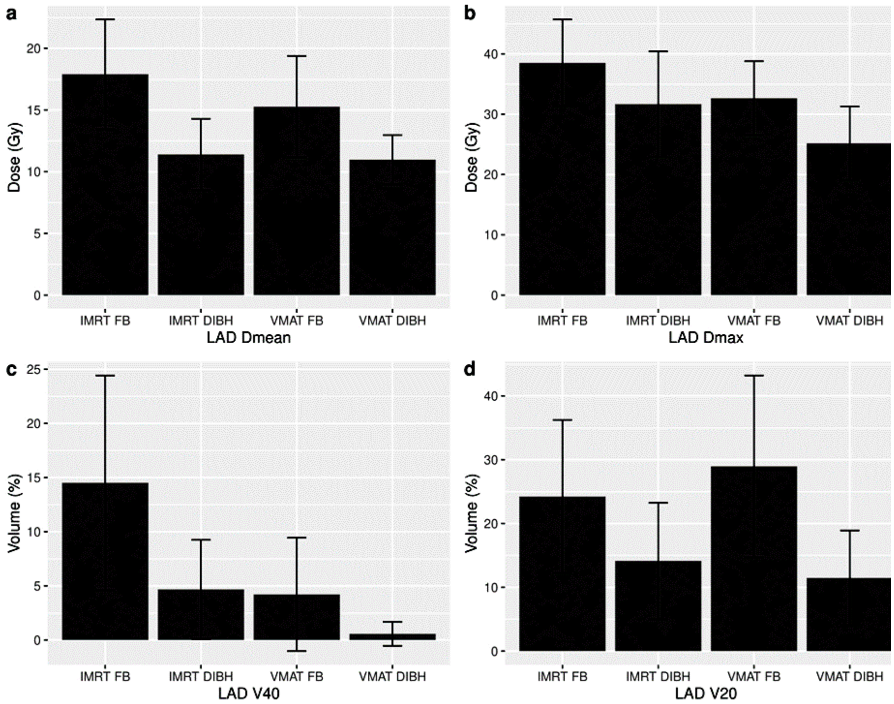

Figure 5. Mean±1.96*Standard error. Graphical view of LAD Dmean **(a)**, Dmax **(b)**, V40 **(c)** and V20 **(d)** values in four different planning techniques. Dmean mean dose, Dmax maximum dose, VX (%) The percent volume of organ receiving X Gy dose, LAD Left anterior descending artery, IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric-modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

RCA: The lowest D_{mean} dose to the RCA was 4.93 Gy and occurred with the IMRT-DIBH plan, and the highest was 11.30 Gy and occurred with the VMAT-FB plan. The lowest D_{max} dose, 6.59 Gy, occurred with IMRT-DIBH, and the highest, 15.20 Gy, occurred with VMAT-FB (tables 2 and 3).

LACM: The lowest D_{mean} dose to the LACM, 4.32 Gy, was seen with the IMRT-DIBH plan, and the highest, 5.73 Gy, was seen with the VMAT-DIBH plan. The lowest D_{max} dose was 4.84 Gy and occurred with the IMRT-DIBH plan, while the highest was 6.12 Gy and occurred with the VMAT-DIBH plan (tables 2 and 3).

LCxA: The lowest D_{mean} dose to the LCxA, 4.48 Gy, occurred with the IMRT-DIBH plan, and the highest, 5.97 Gy, occurred with the IMRT-FB plan. The lowest D_{max} dose of 5.63 Gy occurred with IMRT-DIBH, and the highest D_{max} dose of 7.28 Gy occurred with IMRT-FB (tables 2 and 3).

Ipsilateral lung dose

The lowest D_{mean} dose to the ipsilateral lung was 12.03 Gy and provided by the IMRT-DIBH plan, while the highest was 13.25 Gy and provided by the VMAT-FB plan. V_{20} volume was lowest with the IMRT-DIBH plan (17.57%) and highest with the VMAT-FB plan (18.99%). V_{12} volume was lowest with IMRT-DIBH (28.92%) and highest with VMAT-FB (35.38%), and V_5 volume was lowest with IMRT-DIBH (61.19%) and highest with VMAT-FB (85.41%; figure 6, tables 2 and 3).

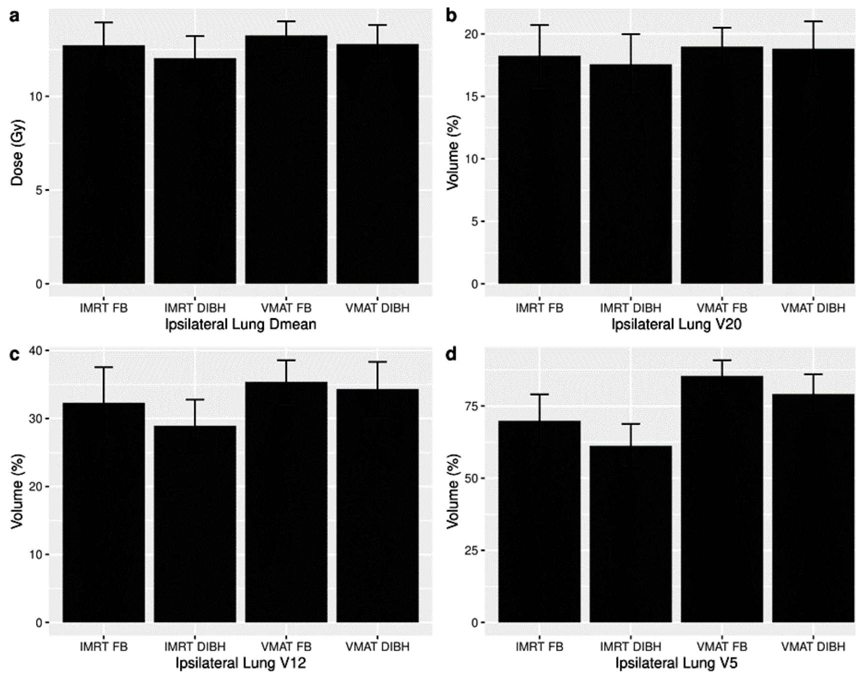

Figure 6. Mean±1.96*Standard error. Graphical view of ipsilateral (left) lung Dmean **(a)**, V20 **(b)**, V12 **(c)** and V5 **(d)** values in four different planning techniques. Dmean mean dose, VX (%) The percent volume of organ receiving X Gy dose, IMRT-FB Intensity-modulated radiotherapy-Free breath, IMRT-DIBH Intensity-modulated radiotherapy-Deep inspiration breath-hold, VMAT-FB Volumetric-modulated arc therapy-Free breath, VMAT-DIBH Volumetric-modulated arc therapy-Deep inspiration breath-hold.

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Other OARs

A comparison of the right lung, total lung, right breast, esophagus and spinal cord doses are given in tables 2 and 3 in detail.

DISCUSSION

RT for breast cancer is an important component of disease management and can reduce the absolute risk of breast cancer mortality, though it can cause serious late side effects in the OARs (i.e., heart and lungs). The effect of DIBH on the heart, LAD, and ipsilateral lung has been demonstrated in previous studies reporting that this technique is superior to the FB technique [16-18]. Darby et al. found a linear relationship between the heart D_{mean} and the rate of major coronary events, which increased by 7.4% per Gy of heart D_{mean} [1]. In the study by Mathieu *et al.* , a decrease of approximately 3 times in the heart D_{mean} and approximately 3.5 times in the LAD D_{mean} was obtained with the DIBH technique compared to FB [19]. In Gaál *et al.*'s study, while significant decreases were observed in the heart D_{mean} and V_{25} (%), LAD D_{mean} and D_{max}, and ipsilateral lung D_{mean} and V_{20} (%) values with the DIBH technique compared to the FB technique ($p < 0.001$), a slight increase was observed in the right breast dose, and the HI value was similar for both techniques [20]. Ferdinand *et al.* prescribed a 40 Gy hypofractionated scheme in 15 fractions with preferred electron treatment to the tumor bed and found a reduction in the heart D_{mean} dose from 4 Gy to 2.4 Gy and the heart V_{10} from 8.9% to 3.4% with DIBH compared to FB. In the same study, LAD D_{mean} was reduced from 12.6 Gy to 8.7 Gy, LAD D_{max} was reduced from 31.9 Gy to 25.8 Gy, and LAD V_{40} was reduced from 0.6% to 0.4% [21]. In the study by Yu *et al.*, FB and DIBH techniques were compared in IMRT and VMAT plans. There was no significant difference between heart and LAD results using DIBH. However, while VMAT was found to have significantly lower ipsilateral lung V_{30} (%), IMRT had significantly lower right lung D2% (Gy), right breast D2% (Gy), and right breast V_5 (%). VMAT-DIBH provided much lower doses than VMAT-FB to almost all OARs, which is in line with the results of our study [22]. Zhang *et al.* compared FB and DIBH techniques in VMAT and found that heart, LAD, left and right lung, and right breast doses were significantly lower in the DIBH technique [23]. In our study, we observed the lowest heart D_{mean}, V_{10}, and V_2 values with the IMRT-DIBH technique but the lowest V_{25} value with the VMAT-DIBH technique. Although post-RT cardiac side effects have been primarily described in relation to heart D_{mean} and tangential fields, the anterior apical portion of the heart is most likely to receive the highest doses [24]. As dose distribution in the heart is not homogeneous, the radiation received by substructures of the heart could be altered with modern techniques. Jacob *et al.* demonstrated that heart D_{mean} was insufficient to predict left ventricle and LAD doses; hence, the doses received by these substructures are necessary when evaluating cardiotoxicity [25]. We also observed inconsistency between heart D_{mean}, left ventricle D_{mean}, and LAD D_{mean}, as heart D_{mean} and left ventricle D_{mean} were lowest with the IMRT-DIBH technique but LAD D_{mean} was lowest with VMAT-DIBH. The IMRT-DIBH technique was also superior for the right atrium and right ventricle. In the current study, regardless of the plan employed, a significant reduction in the amount of radiation received by the heart was achieved when using DIBH compared to FB.

In a recent meta-analysis by Taylor *et al.*, 10 years after RT, the risk of radiation-related lung cancer increased by approximately 11% (95% confidence interval 6–19) per Gy of mean lung dose [2]. Pneumonitis is another possible complication of breast cancer RT that can lead to lung fibrosis several months after treatment [26]. As with radiation-related lung cancer, the risk of pneumonitis increases with increasing lung radiation dose. In this context, while an intermediate dose such as V_{20} is a well-established risk factor for radiation pneumonitis, V_5, often caused by IMRT and VMAT, may also be associated with pneumonitis [27].

In our study, we observed the lowest doses in all parameters for the ipsilateral lung with IMRT-DIBH. Moreover, DIBH significantly reduced ipsilateral and contralateral lung V_5 in both IMRT and VMAT techniques. Radiation-induced coronary artery disease is characterized by ostial stenosis with a significantly higher incidence of severe LACM disease, followed by ostial RCA and LAD stenosis. The location and severity of stenosis directly correlate with the volume irradiated and the dose of the radiation beam [28]. A few studies in the literature have evaluated the RCA, LACM, and LCxA in breast cancer RT [29-31]. However, no comparisons have been made regarding how these vascular structures are affected by the use of FB and DIBH techniques in IMRT and VMAT plans. In the current study, lower doses were observed in all 3 of these vascular structures with IMRT-DIBH. In the DIBH technique, IMRT compared to VMAT , all results except for LACM D_{max} were significantly lower. In the IMRT plans, DIBH elicited lower values than FB in all outcomes, with significance present in LACM D_{mean} and LCxA D_{mean} and D_{max}. In VMAT plans, the RCA dose was lower in the DIBH technique than in the FB technique, while the LACM and LCxA doses were higher in the DIBH technique than the FB technique. Long-term follow-up is required to understand how these differences in coronary artery dose and volume affect the clinical outcome.

Of the limitations of this study, the most obvious is the challenge of contouring the vasculature of the heart. Although relevant atlases and the aid of a radiologist were employed to optimize the contouring, these vascular structures are occasionally seen only faintly on computed tomography sections. Using a 0.5 cm brush pen in the planning system, the arteries were contoured in the sections where they were visible, and automatic joining was used in the other sections.

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CONCLUSION

In RT of patients with left BCS, while IMRT and VMAT provided variable advantages and disadvantages in the doses received by OARs, the DIBH technique provided significant dose reductions in the lung, heart, and all substructures of the heart compared to FB. Based on these results, we recommend using the DIBH technique in addition to the patient-specific IMRT or VMAT plan in RT of patients with left BCS.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Institutional review board approval was obtained for this study. The study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Kayseri City Hospital. Ethics Committee convened on 11.06.2020 and received the protocol number 2020/78.

Authors' Contribution: All authors had full access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization,* AA, SAA, EA, ID; *Methodology*, AA, SAA, EA, SKE, ID; *Investigation,* AA, EA, SKE, ID, YG; *Formal Analysis,* AA, ID, YG; *Writing-Original Draft, Review & Editing,* AA; *Visualization*, AA.

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