Original Article

Optimal radiotherapy modality sparing for cardiac valves in left-sided breast cancer

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Background: The cardiotoxicity caused by radiotherapy is a critical problem in the treatment of patients with breast cancer. The appropriate radiotherapy modality sparing for cardiac valves in left-sided breast cancer has not been well defined. The aim of this study was thus to compare the dosimetric differences in heart and cardiac valves of 3-dimensional conformal radiotherapy (3D-CRT), fixed-field intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT) to find the optimal radiotherapy modality sparing for cardiac valves in patients with left breast cancer.

Methods: From January 5, 2021, to March 15, 2021, 21 patients with left-sided breast cancer postmastectomy were included in this study, and 3 different plans for adjuvant radiation were created using 3D-CRT, IMRT, and VMAT for each patient. All patients received 50 Gy in 25 fractions. The mean dose (D_{mean}) of the heart; percentage volume of the heart receiving ≥5 Gy (V_5), ≥30 Gy (V_{30}), and ≥40 Gy (V_{40}); and the D_{mean} and the near-maximum dose ($D_{0.03cc}$) of cardiac valves were extracted from dose-volume histograms (DVHs) and compared. The correlations in dosimetric factors between cardiac valves and the whole heart were analyzed.

Results: IMRT significantly decreased the values of V_5, V_{30}, V_{40}, and D_{mean} in the whole heart compared to 3D-CRT and VMAT ($P<0.001$). Among the 3 different plans, IMRT had the lowest radiation dose to the D_{mean} and the $D_{0.03cc}$ of the aortic valve (1.27 Gy/1.75 Gy), pulmonary valve (3.44 Gy/6.89 Gy), tricuspid valve (1.02 Gy/1.14 Gy), and mitral valve (0.93 Gy/1.00 Gy). Pearson correlation analysis found that local parameters (D_{mean} and $D_{0.03cc}$) within valves were strongly correlated to the global parameters (V_5, V_{30}, V_{40}, and D_{mean}) of the heart.

Conclusions: This study revealed that IMRT showed the lowest cardiac valves dose compared with 3D-CRT and VMAT in left-sided breast cancer radiotherapy. IMRT might be the optimal modality sparing for cardiac valves in this group of patients. Further studies need to be carried out in order to validate the protective role of IMRT on the cardiac valves.

Keywords: Breast cancer; heart; cardiac valves; radiotherapy modality

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Introduction

Breast cancer is the most frequent carcinoma among women worldwide (1). Radiotherapy for breast cancer is an essential part of adjuvant cancer treatment. Adjuvant radiotherapy reduces breast cancer mortality by one-sixth and local recurrence risk by half for patients with breast cancer (2). However, radiotherapy is associated with long-term cardiac toxicity and in long-term breast cancer survivors, cardiovascular disease after radiation therapy has become the leading cause of non-breast cancer death (3,4). Patients with left-sided breast cancer who underwent adjuvant radiotherapy may have experienced clinically significant cardiac radiation exposure (5) and may be at higher risk of these cardiac complications than patients with right-sided breast cancer. Therefore, the cardiotoxicity caused by radiotherapy in left-sided breast cancer is an important problem that needs to be studied extensively.

It had been reported that the mean heart dose (MHD) was linearly related to the incidence of ischemic heart disease (3,6,7). Therefore, decreasing the MHD is essential for avoiding long-term cardiotoxicity. In recent years, an increasing amount of evidence indicated that the dose of cardiac valves needs to be considered. Some studies have identified the left anterior descending artery (LAD) and the left ventricle (LV) as important parts of the heart that are associated with radiation-induced heart disease (6,8,9). Moreover, compared with right-sided radiotherapy for breast cancer, left-sided radiotherapy has been shown to increase the risk of heart and coronary toxicity (10-13), resulting in excess cardiovascular mortality and morbidity (3,14-16). For precise radiotherapy-induced cardiotoxicity studies, it is necessary to consider the distribution of doses within these cardiac valves in addition to MHD. Therefore, an appropriate technique that could minimize cardiac and substructure doses in breast cancer radiation therapy may be beneficial for breast cancer patients.

Postoperative radiotherapy for left-sided breast cancer is usually delivered using 3-dimensional conformal radiotherapy (3D-CRT), fixed-field intensity-modulated radiation therapy (IMRT), and volumetric-modulated arc therapy (VMAT). Conventional 3D-CRT treatment planning is manually optimized, which indicates that the treatment planner selects all beam parameters, including the quantity, directions, shapes, weights of the beams etc., and the computer calculates the resulting dose distribution (17). IMRT is an advanced technique of high-precision radiotherapy driven by computer-optimized planning that allows modulation of beam intensity within treatment fields to obtain highly conformal dose delivery (18). VMAT is a novel radiation therapy technique that delivers the radiation dose continuously as the treatment machine rotates, which can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues (19). However, the optimal radiotherapy modalities sparing for cardiac valves in left-sided breast cancer is still unclear.

The aim of this study was to evaluate the dosimetric differences of heart and cardiac valves between 3D-CRT, IMRT, and VMAT and to find an optimal postoperative radiotherapy which yielded the least dose exposure to the cardiac valves for patients with left-sided breast cancer. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6633/rc).

Highlight box

Key findings

- Intensity-modulated radiation therapy (IMRT) showed the lowest cardiac valve dose in left-sided breast cancer radiotherapy.

What is known and what is new?

- Radiotherapy is related to cardiac valve toxicity in long-term breast cancer survivors.
- This study explored the optimal radiotherapy modality sparing for cardiac valves in patients with left-sided breast cancer.

What is the implication, and what should change now?

- IMRT might be the optimal modality sparing for cardiac valves in this group of patients. Further studies need to be carried out in order to validate the protective role of IMRT on cardiac valves.

Methods

Patient selection

From January 5, 2021, to March 15, 2021, 21 patients were included in the current study. The age of the included patients ranged from 46 to 68 years at the time of treatment. Patients with any personal history of myocardial or coronary artery disease, echocardiographic abnormalities, or previous radiotherapy to the thorax were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Chongqing University Cancer Hospital Ethics Committee (No. CZLS2022251-A). All methods were carried out in accordance with the approved guidelines. As this was a retrospective analysis of routine data, we requested

and were granted a waiver for individual informed consent from the ethics committee. Patient records/information was anonymized and deidentified prior to analysis.

Immobilization and simulation

Patients were all immobilized in the supine position, with both arms above the head, and head-in-first position with an addition of a 0.8-cm bolus. The bolus was placed to cover the whole chest wall with 2- to 3-cm margins in every direction. The data sets of the computed tomography (CT) scans were obtained utilizing a Philips Big Bore CT scanner (Philips, Amsterdam, the Netherlands) with contrast and a 5-mm slice thickness. The scan scope was from the mandible to the thorax, and the adjacent organs at risk (OARs), such as the heart, lungs, esophagus, trachea, and contralateral breast, were completely covered. All the images were transferred to the Eclipse treatment planning system (TPS; version 15.6, Varian Medical Systems, Inc., Palo Alto, CA, USA) for planning.

Definition of target volumes and OARs

The target volumes and adjacent normal tissues were contoured on the Eclipse TPS. The clinical target volume (CTV) was delineated on each CT data set. The CTV included the chest wall and supraclavicular (SCV) lymph nodes in all patients, +/– the internal mammary lymph nodes and was contoured according to the RTOG consensus. The planning target volume (PTV) was expanded 5 mm based on the CTV and excluded the heart. Then the PTV was retracted 5 mm from the skin and limited posteriorly by the intercostal front. The adjacent OARs (whole heart, ipsilateral and contralateral lungs, esophagus, trachea, spinal cord, and contralateral breast) were contoured. The cardiac valves, cardiac chambers, and coronary vessels were contoured according to the heart atlas reported by Feng *et al.* (20).

Radiotherapy plans

Three different radiotherapy plans (3D-CRT, IMRT, and VMAT) were created based on the CT data sets of each the 21 cases on the Eclipse TPS. Dose calculations without or with dose optimization were performed using 6-MV photon beams generated by a Varian IX device for all 63 plans. The algorithms of dose-volume optimizer and the progressive resolution optimizer were used for IMRT and VMAT dose optimizations, respectively. The anisotropic analytical algorithm was used for the final dose calculations for all plans (21,22).

3D-CRT plans

Since the PTV could be divided into the chest wall and the SCV regions, two 3D-CRT plans were made for the two regions respectively. The plans for the chest wall region comprised 2 opposed tangential open beams with suitable physical wedges. The plans for the SCV region owned 2 opposed tangential open beams plus 1 open beam with the angles of 30°, and the 3 beams were appended with appropriate physical wedges as needed.

IMRT plans

The IMRT plans contained 7 fields overall, including 2 opposite tangential fields (θ_c was used to represent the contralateral tangential angle, and the θ_i represented the ipsilateral tangential angle), 3 surrounding fields located at 10° angles nearby (as the θ_c+10° and the θ_i±10°), and 2 fields located at 330° and 30°, respectively. The angles of the collimator and the position of jaws of the fields at 330° and 30° were adjusted for irradiating the PTV in the SCV region, and similar adjustment was adopted for the field at θ_i to irradiate the whole PTV as well as for the remaining 4 fields to irradiate the PTV in the chest wall region. All the fields adopted the dynamic sliding-window IMRT delivery technique and fixed-jaw technique to deliver radiation doses at a fixed dose rate of 400 monitor units (MUs)/min.

VMAT plans

The VMAT plans contained 5 coplanar arcs overall, including four 60° arcs rotated in clockwise/counterclockwise fashion within the range of [θ_c–10°, θ_c+50°], [θ_c+50°, θ_c–10°], [θ_i+10°, θ_i–50°], and [θ_i–50°, θ_i+10°], and one 50° arc rotated in clockwise fashion from 0° and 50°. The angles of the collimators of the four 60° arcs were designed at 30° or 330°, and the corresponding angle to the 50° arc was set to 0°. The jaws of the 50° arc were adjusted to irradiate only the PTV in SCV regions. All the VMAT plans were optimized and calculated with a maximum dose rate of 600 MUs/min.

The prescribed dose was set as 2 Gy per fraction and a total dose of 50 Gy. For 3D-CRT plans, the prescribed 95% isodose covered at least 95% of the PTV, and the

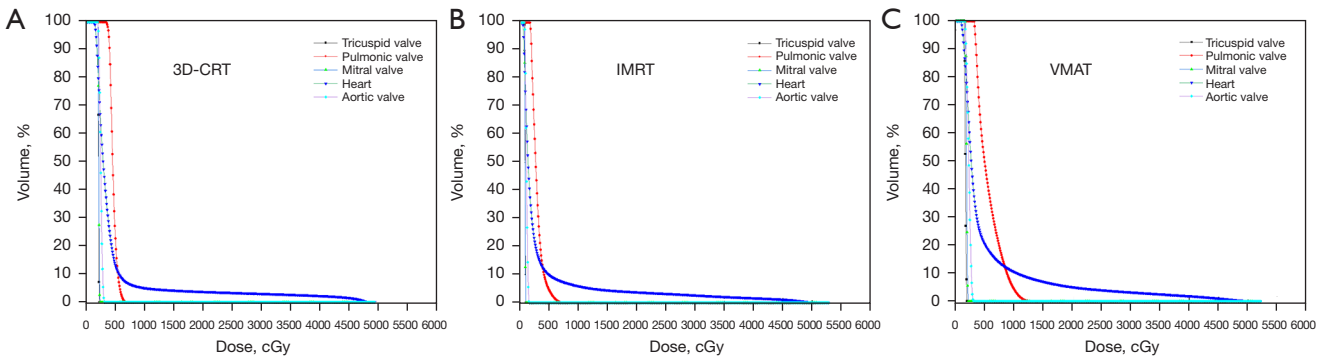

Figure 1 DVH for (A) 3D-CRT, (B) IMRT, and (C) VMAT plans for the same patient. DVH, dose-volume histogram; 3D-CRT, 3D conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

percentage of the PTV receiving a radiation dose greater than 115% of the prescription was less than 2%. For IMRT and VMAT plans, the prescribed 100% isodose covered at least 95% of the PTV, and the percentage of the PTV receiving a radiation dose greater than 110% of the prescription dose was less than 2%. For the 3D-CRT, IMRT, and VMAT plans, the ipsilateral lung V_{20} (percentage of the volume receiving ≥20 Gy) was limited to 35% while the V_5 (percentage of the volume receiving ≥5 Gy) was limited to 75%. The maximum dose of spinal cord was less than 40 Gy. The contralateral breast V_5 was limited to 10%.

Dose evaluation for the whole heart and heart substructures

The data derived from dose-volume histograms (DVHs) of the 63 plans were collected and analyzed. *Figure 1* shows the representative DVHs of the whole heart and cardiac valves in the 3 different plans. For the whole heart, the dosimetric comparative analysis was conducted on the dosimetric/volumetric factors V_5, V_{30}, and V_{40}, and on the near-maximum dose ($D_{0.03cc}$) and mean dose (D_{mean}). This dosimetric analysis also compared the $D_{0.03cc}$ and the D_{mean} of 16 cardiac substructures, including the left atrium, LV, right atrium, right ventricle, left main coronary artery, LAD, left circumflex artery, right coronary artery, ascending aorta, descending aorta, pulmonary artery, superior vena cava, aortic valve, pulmonary valve, tricuspid valve, and mitral valve.

Correlation evaluation

The correlation evaluation was conducted in each radiotherapy modality. The correlations between dosimetric factors of the cardiac valves (D_{mean}, $D_{0.03}$) and the dosimetric and volumetric factors of the whole heart (V_5, V_{30}, V_{40}, D_{mean}, and $D_{0.03cc}$) were analyzed, respectively.

Statistical analysis

Statistical analysis of dosimetric comparisons between groups was carried out using the paired Student *t*-test in SPSS (IBM Corp., Armonk, NY, USA). A P value <0.05 indicated that the difference was statistically significant. Correlation analysis was conducted with the Pearson correlation coefficient (r) with the corresponding P values. A P value <0.05 was necessary to conclude that 2 variables were correlated. An r value from 0 to 0.39 was considered a weak correlation. Values from 0.4 to 0.59, 0.6 to 0.79, and 0.8 to 1.0 were considered moderate, strong, and very strong correlations, respectively (23).

Results

Demographic profile of patients

The mean age of the patients included in the study was 53.7 years, and the median age was 53 years (range, 46 to 68 years). Additionally, 33.3% of the patients were younger than 50 years, and the remainder were older than 50 years. The most common T stage was T1 (42.8%), followed by

Table 1 Demographic profile of patients

Variable	Parameters (N=21)	Patients, n (%)
Age (years)	≤50 years	7 (33.3)
	>50 years	14 (66.7)
T stage (according to AJCC 8th edition)	T1	9 (42.8)
	T2	8 (38.1)
	T3	1 (4.8)
	T4	3 (14.3)
N stage (according to AJCC 8th edition)	N1	12 (57.1)
	N2	7 (33.3)
	N3	2 (9.5)
Stagewise distribution	IIA	5 (23.8)
	IIB	4 (19.0)
	IIIA	6 (28.6)
	IIIB	3 (14.3)
	IIIC	3 (14.3)
Estrogen receptor	Positive	15 (71.4)
	Negative	6 (28.6)
Progesterone receptor	Positive	14 (66.7)
	Negative	7 (33.3)
HER2	Positive	7 (33.3)
	Negative	14 (66.7)
Target region	Left chest wall field and left superior and inferior clavicle field	12 (57.1)
	Left chest wall field and internal mammary field and left superior and inferior clavicle field	9 (42.9)
Neoadjuvant therapy	Yes	11 (52.4)
	No	10 (47.6)

AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2.

T2 (38.1%). N1 (57.1%) was the most common nodal stage, followed by N2 (33.3%). All patients were nonmetastatic (M0). The most frequently encountered stage encountered was stage IIIA (28.6%), followed by stage IIA (23.8%). Other demographic parameters are presented in *Table 1*. Moreover, 52.4% patients received neoadjuvant therapy and 57.1% patients received adjuvant radiotherapy for the field of the left chest wall and left superior and inferior clavicle.

Dose evaluation for the whole heart and cardiac valves

The average radiation dose to the whole heart and cardiac valves are listed in *Table 2*. In comparison with IMRT, 3D-CRT and VMAT increased the values of V_5, V_{30}, V_{40}, and D_{mean} of the whole heart (P<0.001). Among the 3 different plans, IMRT had the lowest radiation dose to the D_{mean} and the $D_{0.03cc}$ of left atrium, right atrium, right ventricle, left main coronary artery, LAD, left circumflex artery, right coronary artery, ascending aorta, pulmonary artery, and superior vena cava (P<0.001).

Compared with IMRT, the values of the D_{mean} of aortic valve, pulmonary valve, tricuspid valve, and mitral valve with 3D-CRT were significantly increased by 118.11%, 77.91%, 134.31%, and 137.63% (P<0.001; P<0.001;

Table 2 Comparison of DVHs of the whole heart and cardiac substructures among the 3D-CRT, IMRT, and VMAT plans

Structures	Substructures	Parameters	3D-CRT (mean ± SD)	IMRT (mean ± SD)	VMAT (mean ± SD)	P value		
						3D-CRT *vs*. IMRT	3D-CRT *vs*. VMAT	IMRT *vs*. VMAT
Whole heart		V_5 (%)	0.17±0.07	0.14±0.06	0.30±0.08	0.000	0.000	0.000
		V_{30} (%)	0.05±0.04	0.02±0.02	0.05±0.03	0.000	0.025	0.000
		V_{40} (%)	0.04±0.03	0.01±0.01	0.03±0.02	0.000	0.000	0.000
		Mean dose (Gy)	5.82±1.85	3.55±1.32	6.62±1.86	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	49.71±1.27	50.69±3.36	51.21±2.26	0.144	0.004	0.171
Chambers	Left atrium	Mean dose (Gy)	2.18±0.22	0.90±0.13	1.51±0.27	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	4.37±1.14	2.85±1.20	4.47±1.94	0.000	0.650	0.000
	Left ventricle	Mean dose (Gy)	7.62±2.47	5.15±2.12	9.09±2.53	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	48.55±1.57	47.17±5.94	49.86±2.99	0.231	0.024	0.004
	Right atrium	Mean dose (Gy)	2.11±0.42	0.80±0.26	1.82±0.66	0.000	0.006	0.000
		$D_{0.03cc}$ (Gy)	4.07±1.87	2.12±1.19	7.27±4.34	0.000	0.000	0.000
	Right ventricle	Mean dose (Gy)	7.49±4.00	4.26±2.24	9.38±3.48	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	46.04±6.34	27.06±6.99	41.90±6.81	0.000	0.000	0.000
Coronary artery	Left main coronary artery	Mean dose (Gy)	3.57±0.54	1.97±0.48	3.30±0.82	0.000	0.019	0.000
		$D_{0.03cc}$ (Gy)	3.82±0.73	2.09±0.52	3.45±0.76	0.000	0.015	0.000
	Left anterior descending artery	Mean dose (Gy)	30.94±9.77	18.87±7.32	30.96±7.91	0.000	0.977	0.000
		$D_{0.03cc}$ (Gy)	46.93±6.55	36.71±8.37	44.91±5.37	0.000	0.053	0.000
	Left circumflex artery	Mean dose (Gy)	2.88±0.29	1.44±0.23	2.40±0.36	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	3.13±0.35	1.62±0.26	2.68±0.37	0.000	0.000	0.000
	Right coronary artery	Mean dose (Gy)	3.15±0.73	1.51±0.55	3.50±1.56	0.000	0.142	0.000
		$D_{0.03cc}$ (Gy)	3.59±0.84	1.88±0.66	4.27±1.91	0.000	0.031	0.000
Great vessels	Ascending aorta	Mean dose (Gy)	2.91±0.36	1.36±0.31	2.61±0.58	0.000	0.001	0.000
		$D_{0.03cc}$ (Gy)	4.13±0.72	2.46±0.82	5.78±1.82	0.000	0.000	0.000
	Descending aorta	Mean dose (Gy)	1.96±0.26	0.87±0.14	1.13±0.15	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	3.31±0.56	1.86±0.30	2.54±1.60	0.000	0.043	0.068
	Pulmonary artery	Mean dose (Gy)	4.56±1.46	2.63±0.81	5.16±1.99	0.000	0.006	0.000
		$D_{0.03cc}$ (Gy)	22.05±17.54	9.45±3.87	20.38±8.20	0.001	0.453	0.000
	Superior vena cava	Mean dose (Gy)	2.32±0.38	0.88±0.19	1.53±0.36	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	2.64±0.45	1.06±0.23	1.86±0.47	0.000	0.000	0.000
Valves	Aortic valve	Mean dose (Gy)	2.77±0.37	1.27±0.28	2.39±0.54	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	3.37±0.63	1.75±0.48	3.46±1.20	0.000	0.545	0.000
	Pulmonic valve	Mean dose (Gy)	6.12±2.88	3.44±1.17	7.68±3.44	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	18.09±16.51	6.89±2.64	15.96±7.00	0.002	0.346	0.000
	Tricuspid valve	Mean dose (Gy)	2.39±0.38	1.02±0.26	2.14±0.62	0.000	0.010	0.000
		$D_{0.03cc}$ (Gy)	2.58±0.48	1.14±0.31	2.53±0.97	0.000	0.741	0.000
	Mitral valve	Mean dose (Gy)	2.21±0.36	0.93±0.22	1.77±0.39	0.000	0.000	0.000
		$D_{0.03cc}$ (Gy)	2.33±0.41	1.00±0.24	1.93±0.41	0.000	0.000	0.000

DVH, dose-volume histogram; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

P<0.001; P<0.001), respectively; the values of the D_{mean} of aortic valve, pulmonary valve, tricuspid valve, and mitral valve with VMAT were significantly increased by 88.19%, 123.26%, 109.80%, and 90.32% (P<0.001; P<0.001; P<0.001; P<0.001), respectively; the values of the $D_{0.03cc}$ of the aortic valve, pulmonary valve, tricuspid valve, and mitral valve with 3D-CRT were significantly increased by 92.57%, 162.55%, 126.32%, and 133.00% (P<0.001; P=0.002; P<0.001; P<0.001), respectively; and the values of the $D_{0.03cc}$ of aortic valve, pulmonary valve, tricuspid valve, and mitral valve with VMAT were significantly increased by 97.71%, 131.64%, 121.93%, and 93.00% (P<0.001; P<0.001; P<0.001; P<0.001), respectively.

Correlation analysis between the heart dose and valves doses

The Pearson correlation coefficient analysis between dosimetric factors of the cardiac valves (D_{mean}, $D_{0.03cc}$) and the dosimetric and volumetric factors of the whole heart (V_5, V_{30}, V_{40}, D_{mean}, and $D_{0.03cc}$) with corresponding P values was performed for 3D-CRT, IMRT, and VMAT, with the relative results being summarized in *Tables 3-5*, respectively. Strong correlations of dosimetric parameters were found between most cardiac valves and the whole heart. Specifically as it relates to the valve dosimetric study, the relationship between the local parameters (D_{mean} and $D_{0.03cc}$) within valves and the global parameters (V_5, V_{30}, V_{40}, and D_{mean}) of the heart were statistically the strongest.

Discussion

For decades, improvements in the curative effects of radiotherapy have resulted in the longer survival time of patients with cancer, and thus the assessment of cardiotoxicity caused by radiotherapy has become increasingly important. The related literature (24-26) has mainly focused on the volumetric dose of the heart, but few studies have examined the cardiac valves specifically. Cardiac valves play a critical role in controlling blood flow through the body. Exposure to radiation increases the risk of cardiac valve damage in breast cancer. Radiotherapy modalities that can decrease the cardiotoxicity have been investigated for a long time. However, the optimal radiotherapy modality sparing for cardiac valves remains unclear. To address this deficit in knowledge, we conducted a comparison of cardiac valve dose among 3D-CRT, IMRT and VMAT in patients with left-sided breast cancer receiving postoperative radiotherapy. The current study revealed that the IMRT had the lowest cardiac valve dose compared with 3D-CRT and VMAT, with better dose distributions and target volume coverage than 3D-CRT. Our findings implied that IMRT might be the optimal modality sparing for cardiac valves in left-sided breast cancer radiotherapy. In addition, correlation analysis demonstrated that the V_5, V_{30}, and D_{mean} of whole heart were strongly associated with cardiac valves dose.

Radiotherapy cardiotoxicity is closely associated with the radiotherapy modality. Compared to 3D-CRT, IMRT has been widely used over the past decade, allowing optimal dose distribution according to individual anatomy (27). It has better dose homogeneity of the target volume and better sparing for the heart and lung. VMAT, as a new radiotherapy technique, was introduced by Otto (28) in 2008 and deliver a intended dose in a single gantry rotation and in a decreased the treatment time compared to IMRT. Numerous studies have compared the influence of the aforementioned 3 modalities on the heart dose distribution. Rastogi *et al.* (29) demonstrated that the MHD in a 3D-CRT arm was significantly higher than that of an IMRT arm (8.96 *vs.* 4.57 Gy; P<0.001). Sudha *et al.*'s study (30) revealed that the MHD value was decreased in the VMAT plan (3D-CRT *vs.* VMAT: 15.78 *vs.* 10.86 Gy). Ma *et al.* (31) conducted a study on a dosimetric comparison of 3D-CRT, IMRT, and VMAT in postoperative radiotherapy for left-sided breast cancer. They found that the MHD in 3D-CRT, IMRT, and VMAT were 7.29, 8.08, and 11.90 Gy, respectively. In our study, we found that the MHD in 3D-CRT, IMRT, and VMAT were 5.82, 3.55, and 6.62 Gy, respectively, which were lower than those of the corresponding values in the 3 studies mentioned above (29-31). Our findings revealed that IMRT had the lowest MHD, and heart V_5, V_{30}, and V_{40} values compared to 3D-CRT and VMAT, which is in line with previous reports (29,32). However, Ma *et al.* (31) reported that the value of MHD in 3D-CRT was lower than that of IMRT and VMAT, which is inconsistent with our finding. This discrepancy may be due to patient heterogeneity, as well as differences in the requirement of planning target coverage and conformal index, constraints for various OARs, etc.

Our findings show that, compared with 3D-CRT and VMAT, IMRT resulted in the lower radiation exposure of the cardiac valves. In this cohort of patients, for 3D-CRT, IMRT, and VMAT, the pulmonary and aortic valves were

Table 3 Correlations of DVH dosimetric parameters between the whole heart and cardiac substructures in the 3D-CRT plan

Structures	Substructures	Parameters	Heart									
			V_5 (%)		V_{30} (%)		V_{40} (%)		Mean dose (Gy)		$D_{0.03cc}$ (Gy)	
			r	P	r	P	r	P	r	P	r	P
Chambers	Left atrium	Mean dose (Gy)	0.609	0.003	0.490	0.024	0.480	0.028	0.556	0.009	–0.086	0.710
		$D_{0.03cc}$ (Gy)	0.134	0.561	0.189	0.411	0.189	0.412	0.153	0.508	–0.438	0.047
	Left ventricle	Mean dose (Gy)	0.867	0.000	0.950	0.000	0.953	0.000	0.943	0.000	0.416	0.061
		$D_{0.03cc}$ (Gy)	0.233	0.309	0.379	0.090	0.413	0.063	0.360	0.109	0.927	0.000
	Right atrium	Mean dose (Gy)	0.874	0.000	0.711	0.000	0.680	0.001	0.791	0.000	0.078	0.738
		$D_{0.03cc}$ (Gy)	0.741	0.000	0.645	0.002	0.615	0.003	0.684	0.001	0.013	0.955
	Right ventricle	Mean dose (Gy)	0.906	0.000	0.895	0.000	0.877	0.000	0.912	0.000	0.265	0.247
		$D_{0.03cc}$ (Gy)	0.354	0.115	0.394	0.077	0.386	0.084	0.388	0.083	0.430	0.052
Coronary artery	Left main coronary artery	Mean dose (Gy)	0.859	0.000	0.730	0.000	0.706	0.000	0.779	0.000	–0.007	0.977
		$D_{0.03cc}$ (Gy)	0.668	0.001	0.542	0.011	0.528	0.014	0.590	0.005	0.083	0.720
	Left anterior descending artery	Mean dose (Gy)	0.784	0.000	0.829	0.000	0.823	0.000	0.831	0.000	0.569	0.007
		$D_{0.03cc}$ (Gy)	0.381	0.089	0.412	0.063	0.401	0.072	0.420	0.058	0.633	0.002
	Left circumflex artery	Mean dose (Gy)	0.603	0.004	0.482	0.027	0.464	0.034	0.513	0.017	–0.111	0.631
		$D_{0.03cc}$ (Gy)	0.585	0.005	0.499	0.021	0.492	0.023	0.528	0.014	–0.051	0.826
	Right coronary artery	Mean dose (Gy)	0.899	0.000	0.766	0.000	0.721	0.000	0.818	0.000	0.046	0.844
		$D_{0.03cc}$ (Gy)	0.825	0.000	0.696	0.000	0.650	0.001	0.743	0.000	0.028	0.905
Great vessels	Ascending aorta	Mean dose (Gy)	0.868	0.000	0.726	0.000	0.690	0.001	0.789	0.000	0.009	0.968
		$D_{0.03cc}$ (Gy)	0.743	0.000	0.512	0.018	0.456	0.038	0.592	0.005	–0.177	0.443
	Descending aorta	Mean dose (Gy)	0.213	0.353	0.161	0.485	0.178	0.440	0.216	0.348	0.209	0.362
		$D_{0.03cc}$ (Gy)	0.033	0.887	0.029	0.902	0.038	0.868	0.046	0.842	0.210	0.361
	Pulmonary artery	Mean dose (Gy)	0.702	0.000	0.592	0.005	0.562	0.008	0.636	0.002	–0.161	0.485
		$D_{0.03cc}$ (Gy)	0.579	0.006	0.501	0.021	0.467	0.033	0.538	0.012	–0.104	0.655
	Superior vena cava	Mean dose (Gy)	0.647	0.002	0.544	0.011	0.529	0.014	0.613	0.003	0.088	0.703
		$D_{0.03cc}$ (Gy)	0.554	0.009	0.419	0.059	0.400	0.072	0.496	0.022	0.080	0.731
Valves	Aortic valve	Mean dose (Gy)	0.861	0.000	0.734	0.000	0.703	0.000	0.793	0.000	0.094	0.686
		$D_{0.03cc}$ (Gy)	0.782	0.000	0.645	0.002	0.610	0.003	0.704	0.000	0.069	0.767
	Pulmonic valve	Mean dose (Gy)	0.720	0.000	0.676	0.001	0.651	0.001	0.702	0.000	0.034	0.883
		$D_{0.03cc}$ (Gy)	0.609	0.003	0.529	0.014	0.499	0.021	0.572	0.007	–0.025	0.914
	Tricuspid valve	Mean dose (Gy)	0.829	0.000	0.759	0.000	0.739	0.000	0.805	0.000	0.196	0.394
		$D_{0.03cc}$ (Gy)	0.829	0.000	0.781	0.000	0.760	0.000	0.815	0.000	0.237	0.302
	Mitral valve	Mean dose (Gy)	0.803	0.000	0.768	0.000	0.764	0.000	0.799	0.000	0.130	0.576
		$D_{0.03cc}$ (Gy)	0.814	0.000	0.774	0.000	0.767	0.000	0.804	0.000	0.146	0.528

DVH, dose-volume histogram; 3D-CRT, 3-dimensional conformal radiotherapy.

Table 4 Correlations of DVH dosimetric parameters between the whole heart and cardiac substructures in the IMRT plan

Structures	Substructures	Parameters	Heart									
			V_5 (%)		V_{30} (%)		V_{40} (%)		Mean dose (Gy)		$D_{0.03cc}$ (Gy)	
			r	P	r	P	r	P	r	P	r	P
Chambers	Left atrium	Mean dose (Gy)	0.544	0.011	0.515	0.017	0.500	0.021	0.543	0.011	0.350	0.119
		$D_{0.03cc}$ (Gy)	0.190	0.409	0.218	0.342	0.237	0.302	0.169	0.463	0.110	0.636
	Left ventricle	Mean dose (Gy)	0.847	0.000	0.955	0.000	0.935	0.000	0.949	0.000	0.732	0.000
		$D_{0.03cc}$ (Gy)	0.529	0.014	0.572	0.007	0.624	0.003	0.583	0.006	0.862	0.000
	Right atrium	Mean dose (Gy)	0.820	0.000	0.528	0.014	0.453	0.039	0.696	0.000	0.370	0.099
		$D_{0.03cc}$ (Gy)	0.717	0.000	0.460	0.036	0.415	0.061	0.582	0.006	0.251	0.273
	Right ventricle	Mean dose (Gy)	0.906	0.000	0.784	0.000	0.620	0.003	0.885	0.000	0.518	0.016
		$D_{0.03cc}$ (Gy)	0.833	0.000	0.687	0.001	0.547	0.010	0.813	0.000	0.641	0.002
Coronary artery	Left main coronary artery	Mean dose (Gy)	0.827	0.000	0.620	0.003	0.523	0.015	0.727	0.000	0.354	0.115
		$D_{0.03cc}$ (Gy)	0.797	0.000	0.667	0.001	0.590	0.005	0.743	0.000	0.504	0.020
	Left anterior descending artery	Mean dose (Gy)	0.805	0.000	0.812	0.000	0.742	0.000	0.857	0.000	0.677	0.001
		$D_{0.03cc}$ (Gy)	0.626	0.002	0.619	0.003	0.600	0.004	0.646	0.002	0.653	0.001
	Left circumflex artery	Mean dose (Gy)	0.489	0.024	0.627	0.002	0.576	0.006	0.602	0.004	0.154	0.506
		$D_{0.03cc}$ (Gy)	0.515	0.017	0.706	0.000	0.668	0.001	0.660	0.001	0.252	0.270
	Right coronary artery	Mean dose (Gy)	0.849	0.000	0.556	0.009	0.487	0.025	0.703	0.000	0.314	0.165
		$D_{0.03cc}$ (Gy)	0.748	0.000	0.478	0.028	0.394	0.078	0.600	0.004	0.220	0.338
Great vessels	Ascending aorta	Mean dose (Gy)	0.696	0.000	0.364	0.105	0.289	0.203	0.522	0.015	0.141	0.543
		$D_{0.03cc}$ (Gy)	0.400	0.072	0.031	0.892	0.003	0.990	0.191	0.407	−0.092	0.692
	Descending aorta	Mean dose (Gy)	0.121	0.600	0.049	0.833	−0.019	0.935	0.141	0.542	0.128	0.581
		$D_{0.03cc}$ (Gy)	0.036	0.877	−0.034	0.885	−0.126	0.588	0.035	0.880	−0.056	0.809
	Pulmonary artery	Mean dose (Gy)	0.587	0.005	0.438	0.047	0.380	0.089	0.517	0.016	0.124	0.593
		$D_{0.03cc}$ (Gy)	0.615	0.003	0.514	0.017	0.433	0.050	0.557	0.009	0.112	0.628
	Superior vena cava	Mean dose (Gy)	0.636	0.002	0.253	0.268	0.176	0.446	0.450	0.041	0.158	0.495
		$D_{0.03cc}$ (Gy)	0.543	0.011	0.139	0.547	0.068	0.768	0.354	0.115	0.141	0.542
Valves	Aortic valve	Mean dose (Gy)	0.776	0.000	0.522	0.015	0.424	0.055	0.656	0.001	0.183	0.428
		$D_{0.03cc}$ (Gy)	0.660	0.002	0.456	0.043	0.382	0.097	0.553	0.011	0.089	0.709
	Pulmonic valve	Mean dose (Gy)	0.720	0.000	0.615	0.003	0.517	0.016	0.669	0.001	0.158	0.493
		$D_{0.03cc}$ (Gy)	0.620	0.003	0.525	0.014	0.446	0.043	0.573	0.007	0.097	0.675
	Tricuspid valve	Mean dose (Gy)	0.776	0.000	0.666	0.001	0.490	0.024	0.743	0.000	0.352	0.118
		$D_{0.03cc}$ (Gy)	0.792	0.000	0.692	0.001	0.524	0.015	0.764	0.000	0.381	0.088
	Mitral valve	Mean dose (Gy)	0.744	0.000	0.855	0.000	0.833	0.000	0.857	0.000	0.487	0.025
		$D_{0.03cc}$ (Gy)	0.774	0.000	0.862	0.000	0.838	0.000	0.877	0.000	0.512	0.018

DVH, dose-volume histogram; IMRT, intensity-modulated radiotherapy.

Table 5 Correlations of DVH dosimetric parameters between the whole heart and cardiac substructures in the VMAT plan

Structures	Substructures	Parameters	Heart									
			V_5 (%)		V_{30} (%)		V_{40} (%)		Mean dose (Gy)		$D_{0.03cc}$ (Gy)	
			r	P	r	P	r	P	r	P	r	P
Chambers	Left atrium	Mean dose (Gy)	0.528	0.014	0.354	0.116	0.344	0.127	0.483	0.027	0.135	0.561
		$D_{0.03cc}$ (Gy)	0.231	0.313	0.152	0.510	0.175	0.448	0.190	0.410	0.079	0.734
	Left ventricle	Mean dose (Gy)	0.837	0.000	0.954	0.000	0.957	0.000	0.925	0.000	0.701	0.000
		$D_{0.03cc}$ (Gy)	0.428	0.053	0.723	0.000	0.722	0.000	0.620	0.003	0.947	0.000
	Right atrium	Mean dose (Gy)	0.839	0.000	0.719	0.000	0.690	0.001	0.826	0.000	0.431	0.051
		$D_{0.03cc}$ (Gy)	0.702	0.000	0.522	0.015	0.499	0.021	0.659	0.001	0.191	0.407
	Right ventricle	Mean dose (Gy)	0.917	0.000	0.810	0.000	0.756	0.000	0.896	0.000	0.435	0.049
		$D_{0.03cc}$ (Gy)	0.711	0.000	0.686	0.001	0.634	0.002	0.707	0.000	0.508	0.019
Coronary artery	Left main coronary artery	Mean dose (Gy)	0.801	0.000	0.664	0.001	0.603	0.004	0.784	0.000	0.370	0.098
		$D_{0.03cc}$ (Gy)	0.731	0.000	0.712	0.000	0.659	0.001	0.767	0.000	0.463	0.035
	Left anterior descending artery	Mean dose (Gy)	0.810	0.000	0.879	0.000	0.864	0.000	0.878	0.000	0.572	0.007
		$D_{0.03cc}$ (Gy)	0.600	0.004	0.730	0.000	0.693	0.001	0.705	0.000	0.692	0.001
	Left circumflex artery	Mean dose (Gy)	0.596	0.004	0.429	0.052	0.437	0.047	0.525	0.015	−0.078	0.738
		$D_{0.03cc}$ (Gy)	0.637	0.002	0.558	0.009	0.575	0.006	0.614	0.003	0.050	0.830
	Right coronary artery	Mean dose (Gy)	0.833	0.000	0.665	0.001	0.629	0.002	0.801	0.000	0.223	0.330
		$D_{0.03cc}$ (Gy)	0.799	0.000	0.613	0.003	0.573	0.007	0.755	0.000	0.153	0.507
Great vessels	Ascending aorta	Mean dose (Gy)	0.816	0.000	0.658	0.001	0.604	0.004	0.796	0.000	0.319	0.158
		$D_{0.03cc}$ (Gy)	0.592	0.005	0.374	0.094	0.304	0.180	0.529	0.014	0.076	0.742
	Descending aorta	Mean dose (Gy)	0.192	0.405	−0.017	0.943	−0.060	0.795	0.098	0.672	−0.357	0.112
		$D_{0.03cc}$ (Gy)	0.017	0.941	−0.080	0.731	−0.145	0.530	0.002	0.993	0.020	0.932
	Pulmonary artery	Mean dose (Gy)	0.627	0.002	0.430	0.052	0.380	0.089	0.568	0.007	0.077	0.740
		$D_{0.03cc}$ (Gy)	0.654	0.001	0.467	0.033	0.417	0.060	0.604	0.004	0.119	0.609
	Superior vena cava	Mean dose (Gy)	0.531	0.013	0.360	0.109	0.298	0.190	0.507	0.019	0.279	0.221
		$D_{0.03cc}$ (Gy)	0.448	0.041	0.279	0.221	0.206	0.370	0.429	0.052	0.263	0.250
Valves	Aortic valve	Mean dose (Gy)	0.863	0.000	0.680	0.001	0.642	0.002	0.820	0.000	0.227	0.322
		$D_{0.03cc}$ (Gy)	0.807	0.000	0.618	0.003	0.598	0.004	0.745	0.000	0.082	0.723
	Pulmonic valve	Mean dose (Gy)	0.694	0.000	0.479	0.028	0.424	0.055	0.623	0.003	0.076	0.744
		$D_{0.03cc}$ (Gy)	0.658	0.001	0.456	0.038	0.402	0.071	0.595	0.004	0.074	0.748
	Tricuspid valve	Mean dose (Gy)	0.825	0.000	0.720	0.000	0.689	0.001	0.801	0.000	0.368	0.101
		$D_{0.03cc}$ (Gy)	0.830	0.000	0.785	0.000	0.769	0.000	0.834	0.000	0.417	0.060
	Mitral valve	Mean dose (Gy)	0.842	0.000	0.788	0.000	0.781	0.000	0.842	0.000	0.452	0.039
		$D_{0.03cc}$ (Gy)	0.813	0.000	0.798	0.000	0.793	0.000	0.838	0.000	0.490	0.024

DVH, dose-volume histogram; VMAT, volumetric modulated arc therapy.

affected more frequently compared to the tricuspid and pulmonary valves. Radiation exposure is related to a risk of radiation-induced heart valve damage. In addition to leaflet retraction, pathologic alterations also include valve fibrosis and, ultimately, calcification (33). The time of this pathological process from radiation exposure to the onset of clinically severe heart valve disease spans a period of 10 to 20 years (34). Previous research revealed that radiation dose, interval from radiation exposure, and the treatment of chemotherapy were associated with the risk of cardiac valves injuries (35). The findings of our study suggested that radiotherapy modalities are a potential influencing factor for cardiac valve injury. Different treatment modalities can produce variable cardiac valve doses in left-sided breast cancers. Compared with the conventional 3D-CRT technique, the dosimetric advantage of IMRT and VMAT did translate into a significant reduction of D_{mean} and $D_{0.03cc}$ to the cardiac valves. However, unexpectedly, IMRT provided the optimal sparing of cardiac valves over the VMAT in this study. VMAT demonstrated higher $D_{0.03cc}$ and mean radiation dose for the cardiac valves. VMAT does have technical and dosimetric strength over IMRT, including better conformity of dose distribution, a reduction in MUs administered, and a reduction in treatment time for more comfortable patient care. This implies that a good treatment plan should achieve a balance between target coverage and critical organ protection.

The cardiac valves play an essential role in the heart but are not routinely contoured in the clinical practice. The radiation dose distribution and toxicity risk to the cardiac valves have been largely ignored in clinical practice and research. Several radiobiological models such as normal tissue complication probability (NTCP) have been developed to estimate the risk of radiotoxicity to normal tissue (36). These models are used in treatment planning to minimize adverse effects from irradiation. However, due to a lack of substructure contouring, these conventional models have been unable to accurately predict the risk of radiation-induced valvular heart disease (VHD) using only conventional heart DVHs. To date, no specific radiation-induced cardiac valvular injury model has been developed. To address this issue, it is urgent to clarify whether MHD or dosimetric/volumetric factors of the heart can accurately predict the radiation doses for cardiac valves. Recently, Naimi *et al.* (37) conducted a study to evaluate whether cardiac valves doses can be safely derived from the MHD or doses to cardiac chambers. MHD and doses to cardiac valves were shown to be significantly correlated, with the Pearson correlation coefficients ranging from 0.51 to 0.63. Consistent with previous study, our results showed that MHD has a strong to very strong correlation with mean valve dose and a moderate to strong correlation with $D_{0.03cc}$ valve dose. The significant correlations were observed in all radiotherapy modalities including 3D-CRT, IMRT, and VMAT. This finding indicates that MHD is a potential predictive factor for cardiac valve dose. Future studies focusing on the development of dose prediction models to predict the risk of heart valve disease are warranted.

The findings in this report are subject to at least three limitations. First, this study was a retrospective study and had a relatively small sample size. Second, for this is a study on radiotherapy planning, the impact of organ motion, including deformation of the heart substructures and the interplay effect of the various actual clinical scenarios on the dose distribution were not considered. Third, the clinical superiority of IMRT over 3D-CRT and VMAT was not validated by the incidence of cardiotoxic events in the patients with left-sided breast cancer who received radiotherapy treatment. Notwithstanding these limitations, this work offers valuable insights into the protection of the cardiac valves through the selection of the optimal radiotherapy modalities in patients with left-sided breast cancer.

Conclusions

In conclusion, IMRT distributed the lowest dose to the cardiac valves as compared with 3D-CRT and VMAT in left-sided breast cancer radiotherapy. The findings indicate that IMRT might be the best technique for optimal modality sparing for cardiac valves in this group of patients. Further studies need to be carried out in order to confirm the relatively protective value of IMRT for the cardiac valves.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6633/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6633/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6633/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Chongqing University Cancer Hospital Ethics Committee (No. CZLS2022251-A). All methods were carried out in accordance with the approved guidelines. As this was a retrospective analysis of routine data, we requested and were granted a waiver of individual informed consent from the ethics committee. Patient records and information were anonymized and deidentified prior to analysis.

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