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Research Article

Evaluation of Heart Substructures as a Function of Dose and Radiation-Induced Toxicities in Left-Sided Breast Cancer Radiotherapy

Ioana-Claudia Costin[1,2] **and Loredana G. Marcu**[1,3,4]

[1]*West University of Timisoara, Faculty of Physics, Timisoara 300223, Romania*
[2]*Emergency County Hospital, Oradea 410167, Romania*
[3]*UniSA Allied Health and Human Performance, University of South Australia, Adelaide, SA 5001, Australia*
[4]*Faculty of Informatics and Science, University of Oradea, Oradea 410087, Romania*

Correspondence should be addressed to Loredana G. Marcu; loredana.marcu@unisa.edu.au

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Background. A group of cardiopathies (ischemic, arrhythmic, and pericardial cardiac events) were shown to be associated with doses received by heart substructures following radiotherapy, alerting about the importance of dosimetric evaluation of cardiac structures besides the heart. The aim of this study was to assess the dosimetry of heart and heart substructures of left-sided breast cancer radiotherapy to evaluate possible radiation-induced complications. *Methods and Materials*. The study enrolled 20 patients treated with 3D-conformal radiotherapy (3DCRT), while intensity-modulated (IMRT) and volumetric-modulated arc radiotherapy (VMAT) plans were simulated for comparative purposes. The organs at risk (OARs) of interest were the heart, ascending aorta, descending aorta, left ventricle, left atrium, right ventricle, right atrium, superior vena cava, inferior vena cava, and pulmonary artery. *Results*. The percentage of left ventricle included in the radiation field was >5% for all plans (8.92% 3DCRT, 8.30% IMRT, and 6.84% VMAT). A strong correlation between mean heart dose and the percentage of left ventricle overlapping with the radiation fields was observed in 3DCRT ($r = 0.784$) and IMRT ($r = 0.755$) plans, and a moderate correlation was shown between tumor volume and the percentage of left ventricle included in the radiation field for all plans. A moderate correlation was observed between body mass index and cardiac structures for the mean dose to the right ventricle ($r = 0.640$) in conformal plans and V_5 of heart ($r = 0.528$) and left ventricle ($r = 0.669$) in volumetric-modulated plans. Additionally, moderate to strong correlations were found between maximum heart distance and heart dose in both conformal and modulated plans. *Conclusions*. Considering possible occurrences of cardiac events during or postradiotherapy, monitoring the heart and its substructures and setting dosimetric thresholds for healthy tissues must be a priority to achieve a personalized and effective treatment.

1. Background

Treatment personalization in breast cancer radiotherapy is a key objective for treatment efficiency. In view of this, the evaluation and management of doses received by the organs at risk (OARs) is critical for the assessment of radiation-induced toxicities and possible long-term effects. Left-sided breast cancer patients require particular attention due to cardiovascular structures adjacent to the treatment field that are likely to be affected by radiation.

Radiation-induced heart conditions are the most frequent treatment-related toxicities in left-sided breast cancer patients and have been widely investigated [1–3]. Besides the heart, cardiac substructures are also being studied lately in the context of dose to OARs [1–3]. Nevertheless, the reported data on the correlation between doses to cardiac substructures and cardiac changes during or post-radiotherapy are limited [4–7].

Some studies suggested that any 1 Gy on the mean heart dose may involve cardiac complications [4] and limiting the

percentage of the volume receiving 5 Gy (from 29.30% to 16.90%) on the left ventricle decreases the possibility of cardiac events [5]. Wang et al. evaluated the correlation between dose received by cardiac OARs (left ventricle, left atrium, right ventricle, right atrium, and heart) and three groups of cardiopathies (pericardial cardiac events, ischemic cardiac events, and arrhythmic cardiac events). The heart, as well as the left and right atrium, showed a strong association with pericardial events ($P < 0.005$), the left ventricle expressed a strong correlation with ischemic events ($P < 0.014$), and a weak association was observed between left and right atrium for arrhythmic events ($P < 0.047$) emphasizing the need for a well-established threshold dose for the occurrence of radiation-induced cardiac events [6].

Others conducted comparative studies between conformal and modulated radiotherapy techniques suggesting that dosimetric advantages depend on the field geometry: standard tangents, tangential intensity-modulated radiotherapy (IMRT), full arcs volumetric-modulated arc radiotherapy (VMAT), and 2 arcs divided into 2 sections VMAT or multiple arcs (VMAT) [7, 8]. For instance, Jin et al. evaluated the difference between the tangential wedged-fields technique, two types of IMRT (tangential and 7 fields IMRT) and VMAT. Mean heart dose appeared to be lower for tangential IMRT (2.2 ± 1.0 Gy) than the classic technique (3.7 ± 2.0 Gy), 7 fields IMRT (4.4 ± 1.9 Gy), and VMAT (4.6 ± 1.7 Gy) concluding better organs at risk sparing when using intensity-modulated techniques with reduced number of fields (tangential IMRT) [7].

Another study conducted by Huang et al. comparatively evaluated three intensity-modulated techniques: 7 beams IMRT, 2 partial arcs VMAT, and helical tomotherapy (HT). The heart showed better protection with the VMAT technique ($D_{\text{mean}} = 3.99 \pm 0.86$ Gy) than with IMRT ($D_{\text{mean}} = 5.53 \pm 1.02$ Gy) or HT ($D_{\text{mean}} = 5.53 \pm 1.02$ Gy); however, the contralateral healthy tissues were better spared with the latter techniques [9], leaving the debate of the best treatment technique for normal tissue sparing unresolved.

To add new quantitative data to the existing literature, the aim of this study was to evaluate the OARs dosimetry of left-sided breast radiotherapy in terms of heart and heart substructures comparatively with three different radiotherapy techniques: standard 3D-conformal radiotherapy using 2 tangential fields, 6 fields intensity-modulated radiotherapy, and 2 semiarcs volumetric-modulated arc radiotherapy. The dosimetric evaluation was performed to determine possible late implications of radiation on heart substructures and subsequent cardiac complications.

2. Methods and Materials

2.1. Patient Selection and Characteristics. The study enrolled 20 female patients with confirmed left-sided breast cancer treated at our department during 2021–2023 with 3D-conformal radiotherapy (3DCRT) using 6 MV Elekta Synergy Platform with Agility multileaf collimator. While patients were treated with conformal plans, IMRT and VMAT plans were also simulated on the Monaco treatment planning system (TPS) version 6.1.2 for dosimetric comparative purposes. The main patient characteristics are presented in Table 1.

2.2. Computed Tomography Simulation and Patient Positioning. Computed tomography (CT) simulation was performed on a Siemens Somatom Definition AS 20 in the supine position on the Quest breast board which allowed different inclinations of the patient, hand and arm holders, a bottom stopper, and knee support. Following the internal protocol, the scanning was performed with 5 mm slices, the isocenter was marked between the last two ribs, and the patients were immobilized on 7.5° board inclination to achieve a parallel position between the sternum and the treatment couch in order to reduce the irradiated volume of the OARs included in the radiation fields.

2.3. Target and OARs Definition. The prescribed dose was 50 Gy in 25 fractions for contoured breast and lymph nodes for patients with positive biopsy. A boost of 10 Gy in 25 fractions was added to the tumor bed (the equivalent dose for OARs evaluation was 66 Gy with integrated boost).

The organs at risk were contoured by one operator (ICC) for all patients to limit any errors, and the target volume was contoured by each patient's attending physician.

The OARs of interest for this study were the heart and the following substructures: ascending aorta (AA), descending aorta (DA), pulmonary artery (PA), left atrium (LA), left ventricle (LV), right atrium (RA), right ventricle (RV), superior vena cava (SCV), and inferior vena cava (IVC) (Figure 1) [11]. 3D reconstruction of heart structures was also evaluated, and the ascending and descending arteries were merged into a single structure: the aortic arch.

2.4. Treatment Planning. Plans for conformal breast irradiation were made with a collapsed cone algorithm using 2 standard tangential fields for heart sparing, whereas, for lymph nodes irradiation, 2 techniques were used depending on the patient's anatomy: APPA (1 anterior field and 1 posterior) or "Y" (2 anterior fields and 1 posterior). For maximum dose control, the field-in-field (FIF) technique was used.

IMRT and VMAT plans were created with Monte Carlo-based algorithms for inverse planning, using 6 fields for IMRT plans and 1 anterior field for lymph nodes irradiation. VMAT plans were created using 2 anterior 45° (1 clockwise and 1 contra-clockwise) and 2 posterior 45° semiarcs with a region of avoidance between them. Plan optimization for modulated techniques was employed by the parallel and serial cost functions for organs at risk and target penalty and quadratic overdose for tumor volume control.

Dose constraints for organs at risk optimization were $V_5 < 40\%$ (V_5 represents the volume within the 5 Gy isodose not to exceed 40% of the prescribed dose); $V_{25} < 10\%$ (V_{25} is the volume within the 25 Gy isodose not to exceed 10% of the prescribed dose); and $D_{39} < 10\,\text{cm}^3$ which represents the volume (cm^3) that receives no more than 39 Gy [12–14]. Maximum, minimum, and mean doses were also assessed for an accurate literature comparison.

Table 1: Patient characteristics.

Patient	Age	Stage	Tumor volume (cm^3)	BMI (kg/m^2)	MHD (mm)	Other therapies besides irradiation
1	51	$T_{1c}N_1M_0$	1219.04*	32.00	31.00	Chemotherapy before RT
2	59	$T_3N_0M_0$	1100.07*	26.80	6.20	Chemotherapy before RT
3	51	$T_2N_1M_0$	993.51*	32.40	21.10	Chemotherapy before RT
4	63	$T_{4b}N_1M_0$	827.06*	31.60	0.00□	Chemotherapy before RT
5	54	$T_2N_1M_0$	986.62ˆ	25.00	6.50	Chemotherapy before RT
6	35	$T_2N_1M_0$	1505.27ˆ	31.70	8.03	Chemotherapy after RT
7	57	$T_2N_0M_0$	1014.47†	27.50	30.60	Chemotherapy after RT
8	67	$T_2N_2M_1$	3035.64†	39.70	22.20	Chemotherapy after RT
9	50	$T_{4d}N_2M_0$	1691.33*	35.80	23.10	Chemotherapy before RT
10	65	$T_{1c}N_0M_0$	1068.29ˆ	24.20	18.00	Chemotherapy before RT
11	49	$T_2N_1M_0$	721.73*	24.20	34.20	Chemotherapy after RT
12	64	$T_2N_1M_0$	1573.90*	35.40	29.10	Chemotherapy before RT
13	66	$T_{4b}N_1M_0$	2048.91†	36.70	33.00	Chemotherapy before RT
14	58	$T_2N_2M_0$	383.61	26.60	30.30	Chemotherapy before RT
15	49	$T_{4b}N_1M_0$	363.39	26.30	0.00□	Chemotherapy before RT
16	76	$T_{4b}N_2M_1$	2977.07*	47.30	30.40	Chemotherapy after RT
17	67	$T_2N_0M_0$	1522.68†	29.70	23.00	Chemotherapy before RT
18	80	$T_3N_1M_0$	276.27	27.30	23.20	Hormone therapy in 2013
19	73	$T_2N_1M_0$	818.08*	27.40	8.30	Chemotherapy before RT
20	40	$T_2N_1M_0$	998.91†	24.80	28.30	Chemotherapy before RT
Mean	58.7		1256.29	30.62	20.33	

*The heart was not included in tangent fields (heart width = 0.00 mm); therefore, the measurement of maximum heart distance was not feasible. RT = radiotherapy treatment, BMI = body mass index, MHD = maximum heart distance. *Breast and lymph nodes tumor volume. ˆBreast, lymph nodes, and boost tumor volume. †Breast and boost tumor volume. Stage [10]: T1c = tumor between 10 and 20 mm. T2 = tumor between 20 and 50 mm, T3 = tumor >50 mm, T4b = ulceration and/or edema of the skin do not meet the criteria for inflammatory carcinoma, T4d = inflammatory carcinoma, N0 = no lymph node metastases, N1 = metastases to ipsilateral level 1, 2 axially lymph nodes, N2 = metastases in ipsilateral axially lymph nodes fixed to one another or to other structures, M0 = no metastases, and M1 = distant metastases larger than 0.2 mm.

2.5. Statistical Analysis. To evaluate the statistically significant results between the treatment techniques for dosimetric comparisons, a paired Student's t-test was employed for P value calculations. The conformal technique was statistically compared to IMRT plans and also to VMAT plans. The threshold for statistical significance was set at $P < 0.05$ [15].

Pearson correlation was employed to evaluate the association between the mean heart dose and the percentage of LV overlapping with the radiation field and also between the tumor volume and the percentage of LV overlapping with the treatment fields. To evaluate other possible factors that may affect the dosimetry of cardiac structures, correlations were determined between body mass index (BMI) and dose parameters (mean and V_5) for the heart and left and right ventricles [15].

Maximum heart distance (MHD) was measured to further strengthen the analysis of factors that lead to increased cardiac doses. MHD was calculated as the maximum width of the heart included in the tangent fields [16]. In addition, any association between MHD and cardiac structure dosimetry was evaluated through Pearson correlations.

3. Results

Dosimetric parameters evaluated for plan approval regarding the outlined OARs (heart and heart substructures) are presented in Table 2.

The difference between 3DCRT, IMRT, and VMAT plans can be observed by evaluating the dose-volume histogram (DVH) statistics, the P values (Table 3), and the isodoses. Figure 2 illustrates the distribution of radiation to the left-sided breast and to OARs based on the prescribed dose.

The percentage of heart substructures overlapping with the initial tangential fields for 3DCRT, the 6-field IMRT, and semiarcs for VMAT is evaluated in Figure 3. Only two substructures overlapped with the radiation fields, namely the right ventricle (<3% of the volume) and the left ventricle (<9% of the volume).

A strong correlation between mean heart dose and the percentage of LV overlapping with the radiation fields was observed in 3DCRT ($r = 0.784$) and IMRT ($r = 0.755$) plans, suggesting a connection between those two variables (Figure 4).

The influence of tumor volume on cardiac structures dosimetry (% of LV included in radiation field) only shows a moderate correlation between these two variables (Figure 5).

A moderate correlation was observed between BMI and cardiac structures for the mean dose to the right ventricle ($r = 0.640$) in conformal plans and V_5 of heart ($r = 0.528$) and left ventricle ($r = 0.669$) in volumetric-modulated plans (Table 4). Furthermore, moderate-to-strong correlations were found between maximum heart distance and heart parameters (mean dose and V_5) in conformal, as well as modulated plans ($r > 0.500$).

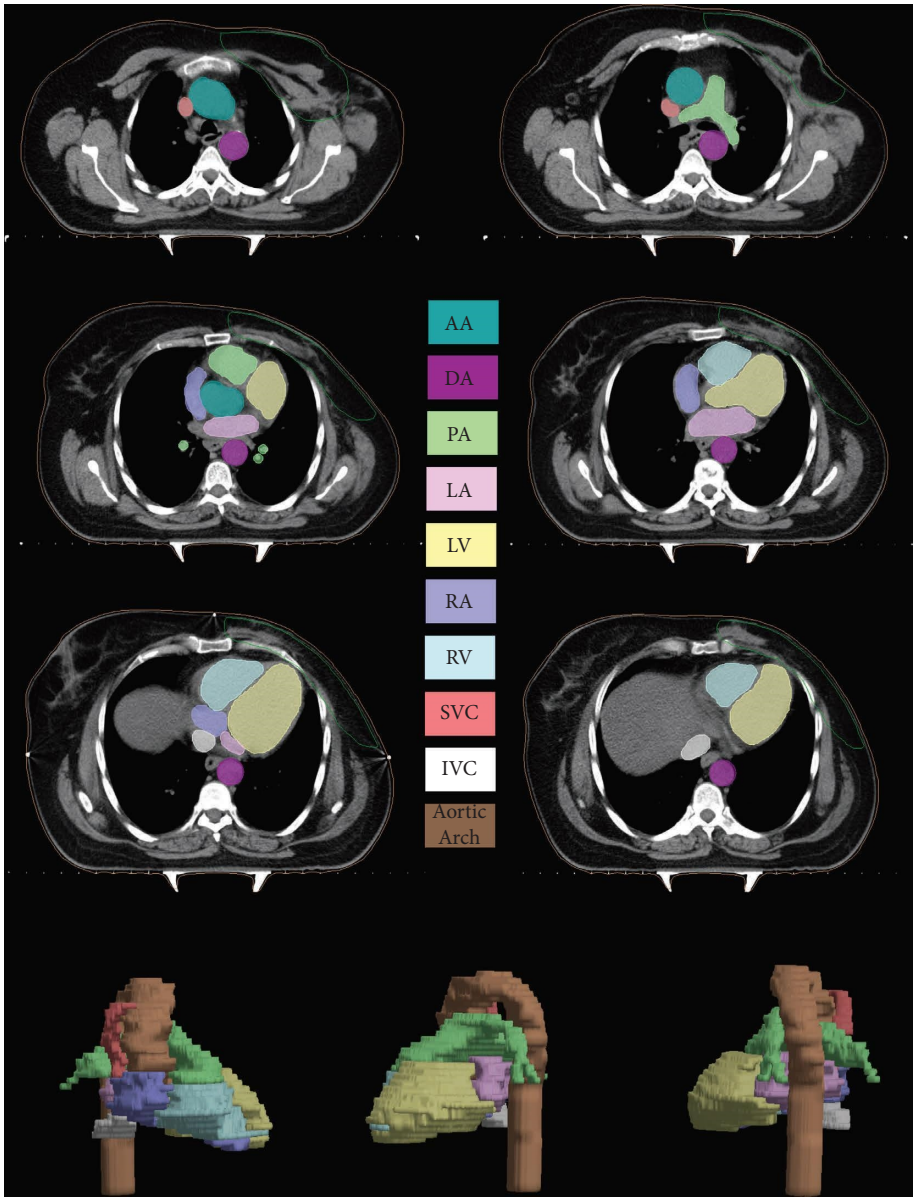

Figure 1: Heart and substructures (AA = ascending aorta, DA = descending aorta, PA = pulmonary artery, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, SVC = superior vena cava, and IVC = inferior vena cava) contoured on Monaco TPS 6.1.2.

4. Discussion

Heart sparing is one of the key aspects of left-sided breast cancer treatment planning because the threshold doses for radiation-induced heart toxicities are still uncertain. Therefore, the choice of treatment technique must be carried out based on OAR dosimetry near the target, by evaluating doses to the heart and its substructures. The aim of this study was to comparatively assess the doses received by the heart and heart structures in left-sided breast cancer patients based on three different treatment techniques: 3DCRT, IMRT, and VMAT.

According to the literature, there are some limited data concerning radiation-induced cardiac events in breast cancer patients (Table 5). Nevertheless, the reported clinical evidence highlights some necessary actions to be taken during treatment planning for better sparing of heart structures that were omitted in the past.

The anatomical localization of postradiotherapy effects was evaluated by Marks et al. using single photon emission computed tomography (SPECT) scans before and after treatment showing that almost all perfusion defects were noticed in the anterior part of the LV which was included in the radiation field [17]. The incidence of new perfusion defects in patients after 6, 12, 18, and 24 months of radiotherapy was reported as a function of LV irradiated volume. According to Marks et al., the incidence of new perfusion defects when 5% of LV volume was included in the tangential fields was between 4–27%, while in patients with over 5% of LV volume, the overlap ranged between 50–63% [17].

Table 2: Dosimetric evaluation of the heart and heart substructures for 3DCRT, IMRT, and VMAT plans.

Dose constraints/treatment technique		Organs at risk									
		Heart	AA	DA	PA	LA	LV	RA	RV	SVC	IVC
$D_{mean} \pm SD$ (Gy)	3DCRT	5.00 ± 1.85	2.24 ± 1.01	1.38 ± 0.50	2.50 ± 0.77	1.52 ± 0.66	6.76 ± 2.01	1.50 ± 0.99	4.29 ± 1.84	1.37 ± 0.83	1.03 ± 0.55
	IMRT	5.26 ± 1.18	4.06 ± 0.97	3.97 ± 1.84	4.19 ± 0.70	2.59 ± 0.82	6.86 ± 1.58	2.18 ± 0.55	5.12 ± 1.78	2.34 ± 0.61	2.35 ± 1.23
	VMAT	5.09 ± 1.13	4.04 ± 1.05	3.66 ± 2.02	4.10 ± 0.77	2.75 ± 0.82	6.51 ± 1.43	2.39 ± 0.38	4.75 ± 1.58	2.89 ± 1.09	2.39 ± 0.78
$D_{max} \pm SD$ (Gy)	3DCRT	48.54 ± 5.54	8.14 ± 9.21	2.90 ± 1.37	19.03 ± 13.89	3.06 ± 1.50	47.66 ± 8.80	4.50 ± 7.55	34.47 ± 16.66	2.01 ± 1.41	1.38 ± 0.94
	IMRT	42.08 ± 2.63	13.20 ± 5.09	10.24 ± 5.43	20.83 ± 9.64	5.38 ± 2.76	39.76 ± 4.77	5.64 ± 5.78	27.89 ± 11.48	3.59 ± 1.47	3.96 ± 2.37
	VMAT	41.12 ± 5.30	11.97 ± 6.43	8.77 ± 6.70	18.49 ± 9.68	5.07 ± 3.30	38.44 ± 6.96	5.22 ± 4.98	25.71 ± 11.50	4.16 ± 1.89	3.85 ± 2.11
$D_{min} \pm SD$ (Gy)	3DCRT	0.78 ± 0.26	1.05 ± 0.35	0.75 ± 0.30	0.71 ± 0.18	0.92 ± 0.30	1.31 ± 0.47	0.89 ± 0.44	1.26 ± 0.60	0.93 ± 0.24	0.76 ± 0.29
	IMRT	1.42 ± 0.38	1.85 ± 0.48	1.53 ± 0.74	1.55 ± 0.27	1.67 ± 0.32	1.97 ± 0.46	1.55 ± 0.33	1.88 ± 0.49	1.77 ± 0.26	1.55 ± 0.63
	VMAT	1.70 ± 0.49	2.03 ± 0.59	1.64 ± 0.77	1.82 ± 0.32	1.97 ± 0.38	2.16 ± 0.49	1.85 ± 0.35	2.12 ± 0.47	2.10 ± 0.32	1.85 ± 0.59
$V_5 \pm SD$ (%)	3DCRT	18.79 ± 8.44	15.52 ± 12.12	0.25 ± 0.26	7.43 ± 8.44	14.98 ± 18.54	28.88 ± 9.94	9.63 ± 14.33	18.32 ± 13.03	38.55 ± 3.25	—
	IMRT	21.16 ± 6.41	22.14 ± 10.84	23.77 ± 13.58	25.06 ± 9.18	11.32 ± 10.80	29.39 ± 8.53	5.43 ± 5.63	23.79 ± 11.95	10.00 ± 16.58	20.31 ± 16.76
	VMAT	19.89 ± 8.27	20.09 ± 11.29	26.29 ± 15.38	20.37 ± 10.13	10.77 ± 14.62	29.12 ± 10.94	4.12 ± 5.55	21.28 ± 12.90	44.02 ± 7.22	9.92 ± 7.91
$V_{25} \pm SD$ (%)	3DCRT	5.14 ± 3.51	1.23 ± 0.87	—	0.20 ± 0.18	—	9.20 ± 5.38	0.98 ± 0.21	2.97 ± 3.23	—	—
	IMRT	3.97 ± 2.55	—	1.64 ± 0.21	0.52 ± 0.83	—	6.71 ± 5.06	0.63 ± 0.25	3.61 ± 3.71	—	—
	VMAT	3.33 ± 2.20	0.11 ± 0.09	10.68 ± 1.21	0.84 ± 1.90	—	5.26 ± 3.54	—	2.29 ± 2.91	—	—
$D_{39} \pm SD$ (cm^3)	3DCRT	22.49 ± 18.91	0.02 ± 0.22	—	0.02 ± 0.01	—	13.80 ± 12.67	—	1.91 ± 2.01	—	—
	IMRT	2.80 ± 4.97	—	—	0.03 ± 0.05	—	1.91 ± 3.24	—	0.38 ± 0.05	—	—
	VMAT	1.88 ± 2.64	—	—	1.02 ± 0.51	—	1.26 ± 2.39	—	0.36 ± 0.42	—	—

SD = standard deviation, AA = ascending artery, DA = descending artery, PA = pulmonary artery, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, SVC = superior vena cava, IVC = inferior vena cava, D_{mean} = mean of the prescribed dose, D_{min} = minimum of the prescribed dose, D_{max} = maximum of the prescribed dose*, $V_{5(25)}$ = % of volume receiving more than 5 Gy (25 Gy), and D_{39} = volume receiving no more than 39 Gy. *The prescribed dose was 50 Gy in 25 fractions for lymph nodes and breast and 10 Gy in 25 fractions for integrated boost. The equivalent dose to 2 Gy/fractions of the prescribed dose was 66 Gy.

Table 3: *P* value calculation between conformal and modulated techniques.

Evaluated parameter	Heart	AA	DA	PA	LA	LV	RA	RV	SVC	IVC
3DCRT vs IMRT										
D_{mean}	0.443	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.341	**0.006**	**0.017**	**<0.01**	**0.001**
D_{max}	**0.001**	**0.014**	**<0.01**	0.404	**0.001**	0.086	0.082	**0.012**	**0.001**	**<0.01**
D_{min}	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
V_5	0.191	**<0.01**	**<0.01**	**<0.01**	0.194	0.785	0.221	**0.021**	0.982	0.054
V_{25}	0.188	—	—	0.307	—	0.147	—	0.555	—	—
D_{39}	**0.001**	—	—	—	—	**0.002**	—	0.241	—	—
3DCRT vs VMAT										
D_{mean}	0.781	**<0.01**	**<0.01**	**<0.01**	**<0.01**	0.847	**0.001**	0.172	**<0.01**	**<0.01**
D_{max}	**<0.01**	**0.022**	**0.001**	0.797	**0.012**	**0.023**	0.396	**0.001**	**<0.01**	**<0.01**
D_{min}	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
V_5	0.467	**<0.01**	**<0.01**	**<0.01**	0.110	0.909	0.241	0.229	—	0.087
V_{25}	**0.009**	—	—	0.454	—	**0.001**	—	0.392	—	—
D_{39}	**0.001**	—	—	—	—	**0.001**	—	0.345	—	—

AA = ascending artery, DA = descending artery, PA = pulmonary artery, LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, SVC = superior vena cava, IVC = inferior vena cava, D_{mean} = mean of the prescribed dose, D_{min} = minimum of the prescribed dose, D_{max} = maximum of the prescribed dose*, $V_{5(25)}$ = % of volume receiving more than 5 Gy (25 Gy), and D_{39} = volume receiving no more than 39 Gy. *The prescribed dose was 50 Gy in 25 fractions for lymph nodes and breast and 10 Gy in 25 fractions for integrated boost. The equivalent dose to 2 Gy/fractions of the prescribed dose was 66 Gy. Statistically significant values are bolded.

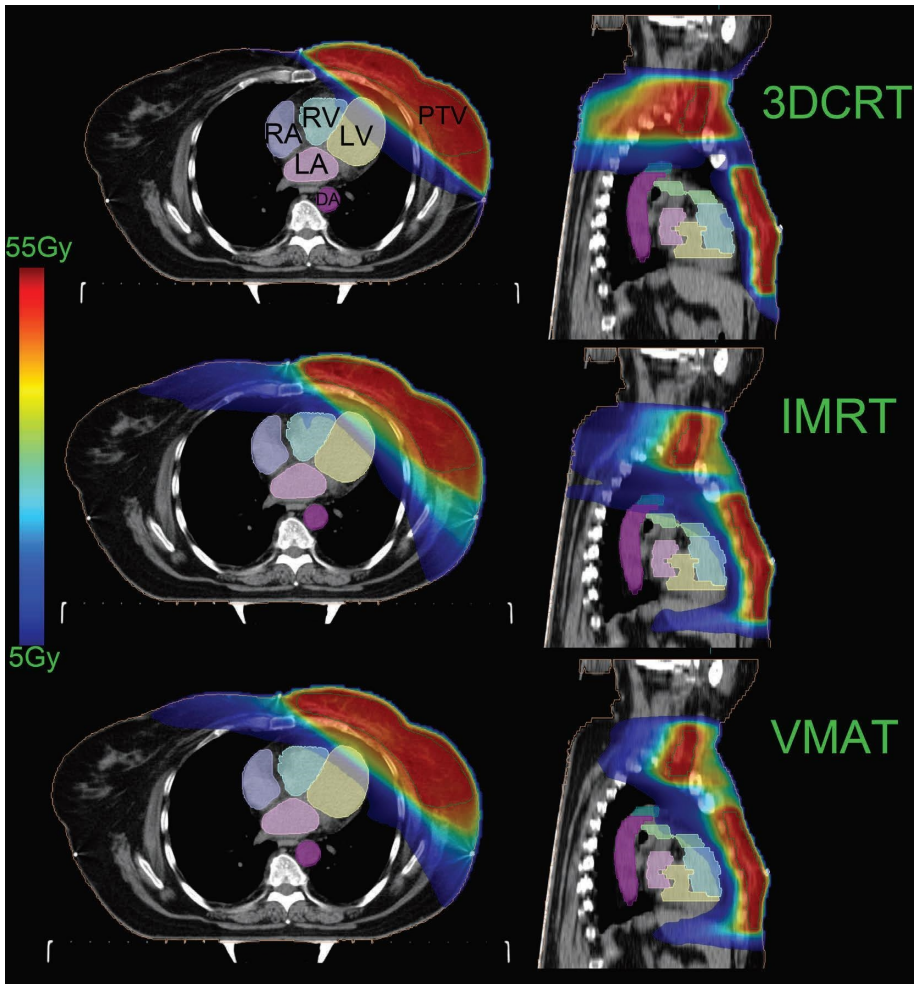

Figure 2: Dose distribution for 3DCRT, IMRT, and VMAT plans (LV = left ventricle, LA = left atrium, RV = right ventricle, RA = right atrium, DA = descending artery, and PTV = planning target volume). The isodose evaluation interval was set within the 5 Gy low dose region and the 55 Gy high dose threshold.

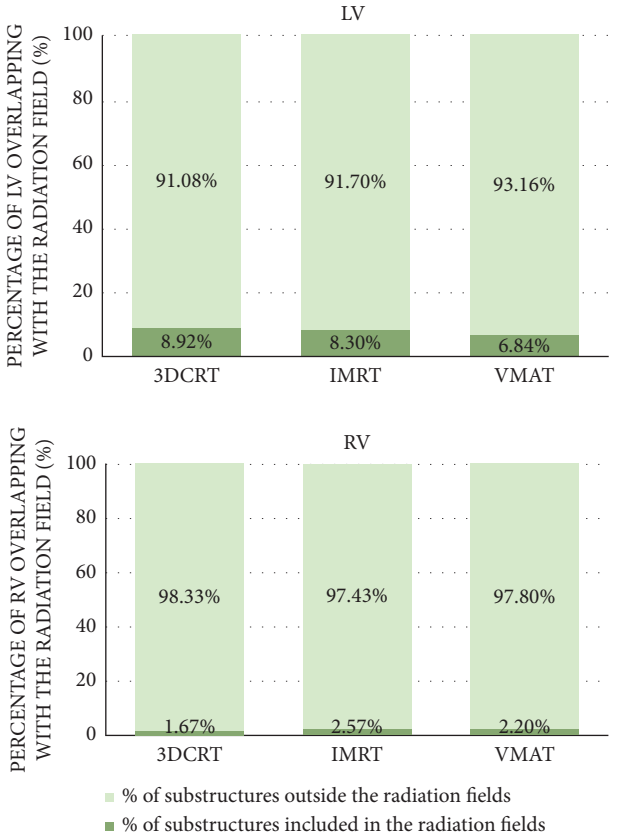

Figure 3: The percentage of heart substructures (RV = right ventricle and LV = left ventricle) overlapping with the radiation fields for 3DCRT, IMRT, and VMAT plans.

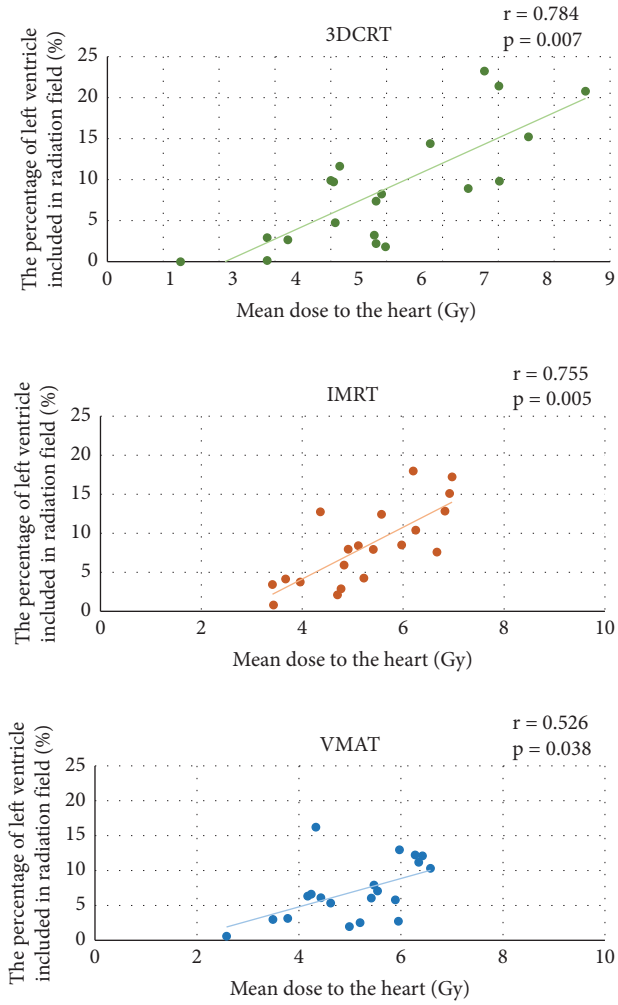

Figure 4: Pearson correlation between mean heart dose and the percentage of left ventricle included in the radiation field, where r is the Pearson correlation coefficient, and the P value illustrates the statistical significance (the threshold was set at $P < 0.05$).

In our study, the mean percentage volume included in treatment fields for LV was over 5% for 3DCRT, IMRT, and VMAT plans, which might be a warning for the occurrence of perfusion defects for evaluated patients. A strong correlation (3DCRT, $r = 0.784$ and IMRT, $r = 0.755$) and a moderate correlation (VMAT, $r = 0.526$) between the above-mentioned variables were observed, suggesting a linear increase of mean heart dose along with the escalation of the overlapping LV volume. The association between tumor volume and the percentage of LV overlapping the irradiation field resulted in a moderate correlation for all three techniques.

The mean dose to the LV across the 20 patients reported in our study was 6.76 ± 2.01 Gy for conformal plans, 6.86 ± 1.58 Gy for IMRT, and 6.51 ± 1.43 Gy for VMAT, noting no statistically significant difference between the 3DCRT plans and those with modulated intensity ($P = 0.341$ for 3DCRT vs IMRT and $P = 0.847$ for 3DCRT vs VMAT). Skyttä et al. estimated 2 thresholds for mean LV dose evaluated after an average of 9 months postradiotherapy. The study showed an increase from the baseline (5 ng/l) of troponin T serum (hscTnT) in 21% (12/58) of patients who had 6.70 Gy mean LV dose and a stable hscTnT value (<5 ng/l) in 79% (46/58) of patients with mean LV dose of 4.50 Gy [19]. Moreover, the mean heart dose of those 12 patients with increased biomarker levels was 4 Gy. Troponin T is an established biomarker of cardiac damage due to ischemic heart disease. Also, it can detect heart failure and LV hypertrophy [19]. In our study, the mean LV exceeded 6 Gy for all treatment techniques, while the mean heart dose was higher than 4 Gy (5 ± 1.85 Gy for 3DCRT, 5.26 ± 1.18 Gy for IMRT, and 5.09 ± 1.13 Gy for VMAT plans) for all treatment techniques, which according to Skyttä et al. leads to an increase in hscTnT which might, in turn, increase the risk of cardiac damages after radiotherapy in 21% of patients [19].

The mean heart dose established by Darby et al. as a threshold was 6.60 Gy stating that the occurrence rate for major coronary events increases by 7.4% for every 1 Gy increase in the mean radiation dose delivered [4]. This statement is also confirmed by Van den Bigaard et al. which reported a 16.5% increase in cumulative incidence for acute coronary events [5]. In our study, the mean heart dose is under 6.60 Gy for all treatment techniques; however, if we consider V_5 for LV ($28.88 \pm 9.94\%$ for 3DCRT, $29.39 \pm 8.53\%$ for IMRT, and $29.12 \pm 10.94\%$ for VMAT plans), the values from the current study are similar to those reported by Van

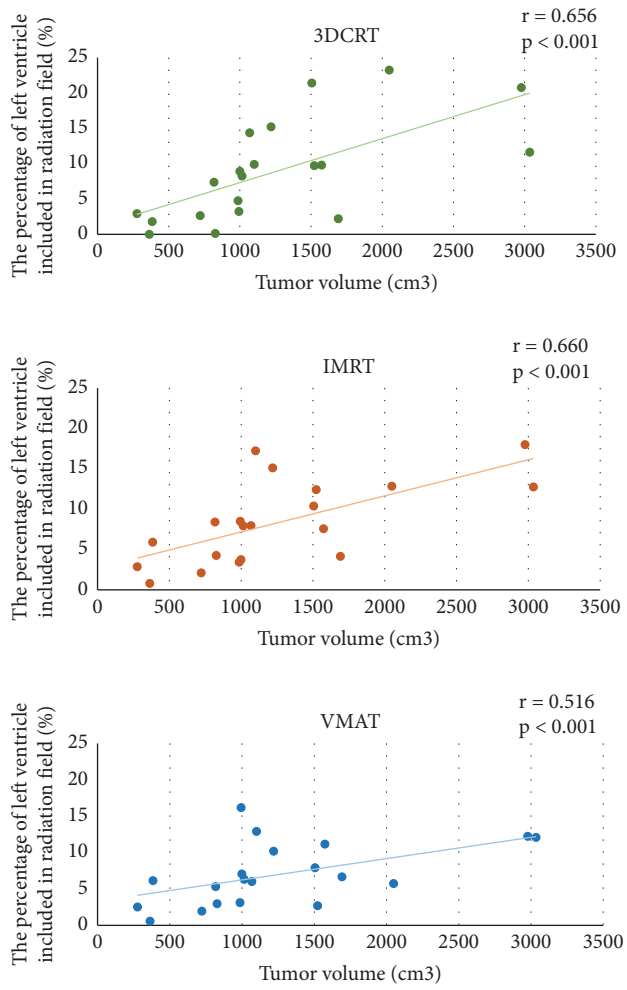

Figure 5: Pearson correlation between tumor volume and the percentage of left ventricle included in the radiation field, where r is the Pearson correlation coefficient, and the P value illustrates the statistical significance (the threshold was set at $P < 0.05$).

Table 4: Pearson correlation coefficient evaluated between BMI and cardiac structures for all treatment techniques.

r	BMI vs cardiac dosimetry			MHD vs cardiac dosimetry		
	3DCRT	IMRT	VMAT	3DCRT	IMRT	VMAT
D_{mean} heart	0.355	0.310	0.343	**0.764**	0.465	**0.588**
V_5 heart	0.327	0.332	**0.528**	0.497	0.462	**0.549**
D_{mean} LV	0.219	0.022	0.109	**0.783**	**0.587**	**0.753**
V_5 LV	0.198	0.318	**0.669**	**0.517**	**0.755**	**0.658**
D_{mean} RV	**0.640**	0.381	0.261	0.574	0.405	0.332
V_5 RV	0.048	0.356	0.391	0.492	0.461	0.390

D_{mean} = mean dose, V_5 = % of volume receiving more than 5 Gy, LV = left ventricle, RV = right ventricle, r = Pearson correlation coefficient, BMI = - body mass index, and MHD = maximum heart distance. Statistically significant values are bolded.

den Bigaard et al. (29.30%) for the occurrence of coronary events [5].

Hotca et al. evaluated the radiation effects on SVC substructure considering the minimum dose (D_{min}) as a predictor for electrocardiogram (ECG) changes [20]. The study concluded that by reducing the minimum SVC dose from 35 Gy to 10 Gy (lung irradiation with dose prescription >50 Gy), it would lead to a 4% reduction (from 16% to 12%) in the cumulative incidence of nonspecific ECG abnormalities (not specifically signaling any medical condition). In our study, D_{min} was 0.93 ± 0.24 Gy, 1.77 ± 0.26 Gy, and 2.10 ± 0.32 Gy for 3DCRT, IMRT, and VMAT plans, respectively, indicating minimum or no risk of radiation-induced ECG abnormalities based on the results reported by Hotca et al. [20].

According to Jacobse et al., body mass index (BMI) could also be used as a predictor of the occurrence of cardiac events. Their results on the risk of myocardial infarction as a function of radiation dose in breast cancer survivors showed that the rate of myocardial infarction increases linearly with the mean heart dose, with BMI >30 being an individual patient-related risk factor significantly correlated with an increased infarction rate [21]. In our study, the mean BMI was 30.62 with 9 patients (45%) exceeding 30 kg/m^2. In addition, because a moderate correlation was observed between BMI and cardiac dosimetric parameters in 3DCRT and VMAT plans (left ventricle V_5: $r = 0.669$, heart V_5: $r = 0.528$, and right ventricle mean dose: $r = 0.640$), these results can indicate possible cardiac complications for patients with increased BMI. However, another study that evaluated body mass index as a predictor for cardiac complications identified no statistically significant correlations [22]. Given the inconclusiveness of studies to date, the correlation between BMI and dose to cardiac structures should be an aspect to be considered in future studies to assist with the identification of subsequent cardiopathies in patients at risk.

Another predicting factor for postradiotherapy cardiac events to be accounted for is the maximum heart distance. Pattanayak et al. performed a statistical correlation between this parameter and mean heart dose and suggested a positive correlation for these two variables ($r = 0.849$ and P value <0.001) [23]. In our study, MHD strongly correlated with mean heart and LV dose (3DCRT heart D_{mean} $r = 0.764$; LV D_{mean} $r = 0.783$; VMAT LV D_{mean} $r = 0.753$). Another strong correlation between dose and MHD was observed for V_5 in the left ventricle for IMRT plans ($r = 0.755$). Similar results were reported by other studies investigating doses to cardiac structures after left-sided breast cancer irradiation [16, 24].

Considerable statistical differences ($P < 0.05$) between 3DCRT plans and those with modulated intensity were observed in our study for the V_5 parameter. For example, V_5 in IMRT and VMAT plans (AA, DA, PA, and RV substructures) and D_{max} (SVC and IVC substructures) showed higher values than that in 3DCRT plans. The largest difference between conformal and intensity modulated plans was observed for DA structures: +26.04% IMRT and +23.52% VMAT compared to 0.25% 3DCRT. However, VMAT plans spared the heart and LV in terms of V_{25} parameter: 3.33% heart and 5.26% LV compared to 5.14% heart and 9.20% LV for conformal plans.

Due to the fact that 2 tangent fields were used in the construction of 3DCRT plans, the 5 Gy isodose (Figure 2)

Table 5: Literature data reporting radiation-induced cardiac events in breast cancer patients.

Ref.	Time to effects	Heart or substructure dose	Effect
Marks et al. [17]	6–24 months	<5% vs ≥5% of the left ventricle was included in the radiation field	Perfusion defects were seen in 10–20% vs 50–60% of patients
Erven et al. [18]	Immediately after treatment and 2 months after treatment	Left apical ventricular segment >3 Gy vs <3 Gy	Significant decrease in strain expressed as a decrease in systolic myocardial deformation
Darby et al. [4]	Within 20 years or within the first 4 years posttreatment	Heart $D_{mean} = 6.60$ Gy	The rate of major coronary events increased by 7.4% for each 1 Gy in the mean radiation dose delivered to the heart
Skyttä et al. [19]	Average of 9 months after treatment	Heart D_{mean}: 4 Gy vs 2.80 Gy LV D_{mean}: 6.70 Gy vs 4.50 Gy	Increase of serum troponin $T > 30\%$
Van den Bigaard et al. [5]	Within 9 years of posttreatment	Per 1 Gy heart D_{mean} LV $V_5 = 29.30\%$ vs 16.90%	16.5% increase in cumulative incidence for acute coronary events Acute coronary event vs no

LV = left ventricle, V_5 = % of volume receiving more than 5 Gy, and D_{mean} = mean dose.

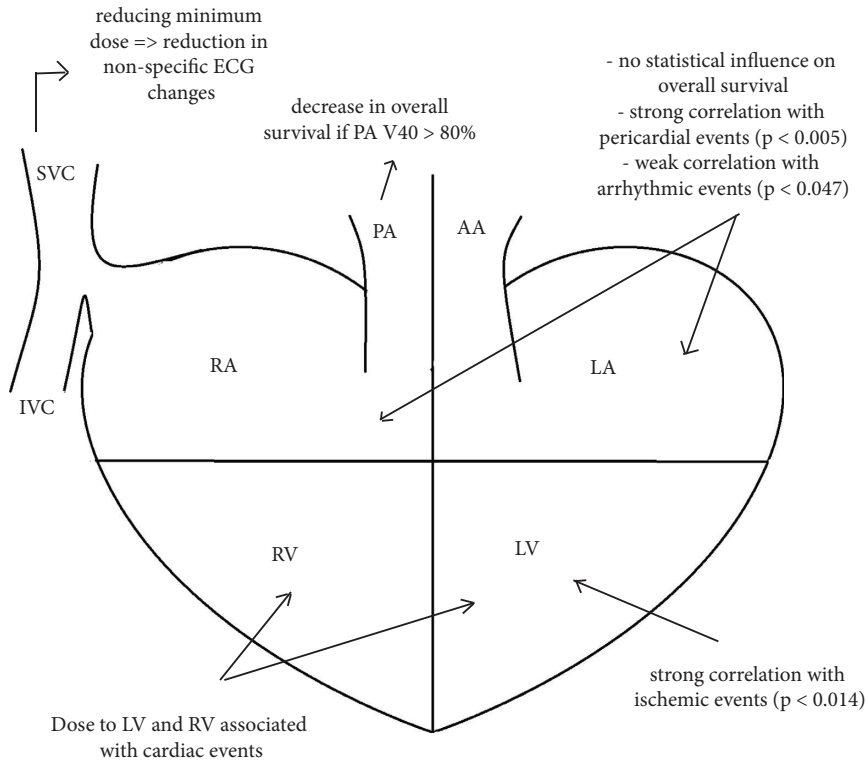

Figure 6: Radiation-induced effects on heart substructures. Representation based on data from [6, 20, 25, 26].

spared healthy tissue irradiation near the breast area, but in the irradiation of supraclavicular lymph nodes (APPA or "Y" technique was used), the spinous processes were covered by the isodose and also reached the jaw. At the same time, high doses touched the LV anterior part and irradiated the structure posteriorly. Comparing 3DCRT isodoses with IMRT and VMAT plans, it was observed that low doses irradiated the anterior region of the contralateral breast avoiding the heart substructures due to the algorithm optimization through cost functions. In IMRT plans, the spinous processes are also irradiated with low doses as in 3DCRT plans. Regions with high doses were better optimized with IMRT than with VMAT, spotting the homogeneity in the anterior region of lymph nodes. However, the posterior region, as well as the spinal cord, was spared by low-dose irradiation delivered by VMAT, possibly due to the chosen geometry (using semiarcs with a region of avoidance).

The dosimetric data from our study can be compared with the study conducted on 30 patients by Ahmad et al. which compared conformal and modulated plans. The conclusions that emerged from the study were that low doses remain a dosimetric concern for intensity-modulated techniques suggesting a lower V_5 for conformal plans [8]. The low dose parameter (V_5) for heart in our study showed a smaller value for conformal plans (18.79% 3DCRT, 21.16% IMRT, and 19.89% VMAT) with no statistically significant difference between conformal and modulated plans ($P > 0.05$). On the other hand, for V_{25} and D_{39}, the values are lower in modulated plans with significant statistical differences between 3DCRT and IMRT for D_{39} ($P = 0.01$) and between 3DCRT and VMAT for both parameters ($P = 0.09$ for V_{25} and $P = 0.01$ for D_{39}).

Figure 6 shows an illustrative collation of postirradiation effects on OARs nearby tumor volume, emphasizing the necessity of contouring several heart structures in left-sided breast cancer patients undergoing radiotherapy [17–19].

One limitation of our study is the relatively small patient cohort evaluated; therefore, statistical calculations and reported data should be interpreted in this context. There are, however, other studies with a similarly small number of patients enrolled, such as the study led by Erven et al. [18] which are still valuable regarding the reported data for LV sparing and heart toxicities, considering the scarce literature on the subject. Another limitation is the imaging system used in our department for patient verification (portal images) which offers no interpretation of cardiac changes during treatment that would allow the identification of the associated dose. However, different board inclinations for patient immobilization on CT simulation for heart sparing and frequent postradiotherapy checkups are employed. While our study evaluated the radiation doses received by cardiac structures conjecturing about potential cardiovascular effects, chemotherapy received by most of these patients might inflict additional cardiac events, which were not taken into account here.

The key observations and recommendations derived from the current study are highlighted as follows:

(i) Low-dose regions in 3DCRT are created around the target volume through the use of tangent fields leading to the sparing of cardiac structures

(ii) The main dosimetric differences between 3DCRT and IMRT/VMAT plans were identified on cardiac substructures from the vicinity of the tumor volume (mainly left and right ventricles)

(iii) The volume of left ventricle included in the radiation field is strongly associated with mean heart dose escalation

(iv) Parameters that pinpoint towards possible cardiac complications (body mass index, maximum heart distance, and tumor volume size) must be taken into account during treatment planning

(v) Conformal planning might be adequate for left-sided breast cancer radiotherapy despite the widespread use of intensity-modulated techniques

(vi) The choice of treatment technique in radiotherapy should be based on patients' cardiovascular risks

(vii) Cardiac substructures should be contoured additionally to the heart in view of a more complex dosimetric assessment and patient monitoring

5. Conclusions

Considering the thresholds evaluated by other studies for cardiac toxicities and the values presented by our study which indicated the likely occurrence of cardiac events and monitoring heart changes with superior imaging systems during therapy, as well as long-term posttreatment monitoring, are necessary tasks to increase quality of life among left-sided breast cancer patients treated with radiotherapy.

Contouring several cardiac structures and long-term monitoring of their evolution would be an advantage in identifying the threshold doses for the other critical structures, such as ascending aorta (AA), descending aorta (DA), right atrium (RA), left atrium (LA), superior vena cava (SVC), and inferior vena cava (IVC), both for tissue sparing and for preventing possible acute or late cardiac events.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study did not require the approval of the institutional board as it did not enroll patients particularly for the study. This work analysed the data of patients that have been treated as per the normal medical protocol without any change induced by this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed to the study's conception and design and read and approved the final manuscript. Data collection and analysis were performed by ICC, original draft preparation was written by ICC and LGM, and reviewing and editing were performed by ICC and LGM.

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