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The Cardiac Effects of Radiotherapy on Women with Breast Cancer Based on Laterality

Azin Alizadehasl [1], MD; Majid Maleki [2], MD; Feridoun Noohi [3], MD; Sara Adimi [4], PhD; Seyed Amirhossein Emami [5], MD; Seyed Asadollah Mousavi [6], MD; Robab Anbiaie [7], MD; Payam Azadeh [8], MD; Hosein Kamranzadeh Fumani [6], MD; Soraya Salmanian [9], MD; Behshid Ghadrdoost [10], PhD; Khadije Mohammadi [11], MD; Shirin Habibi Khorasani [1,*], MD

[1] Cardio-Oncology Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, IR Iran
[2] Echocardiography Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, IR Iran
[3] Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Tehran, IR Iran
[4] Department of Exercise Physiology, Central Tehran Branch, Islamic Azad University, Tehran, IR Iran
[5] Department of Medical Education, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, IR Iran
[6] Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, IR Iran
[7] Department of Radiotherapy, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[8] Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[9] Oncopathology Research Center, Faculty of Medicine, Iran University of Medical Sciences, Tehran, IR Iran
[10] Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[11] Cardiovascular Research Center, Kerman University of Medical Sciences, Kerman, IR Iran

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ABSTRACT

Background: Recent advances in the early detection and management of breast cancer have conferred longer patient survival. Breast irradiation-induced cardiotoxicity has been associated with a decrease in the echocardiographic markers of myocardial function and an increase in cardiac mortality.

Objectives: This study aimed to determine the cardiac effects of radiotherapy on patients with breast cancer based on cancer laterality.

Methods: The present study assessed the records of 72 consecutive women with breast cancer who were referred to the Cardio-Oncology Department of Rajaie Cardiovascular Medical and Research Center between April 2017 and September 2020 and had baseline echocardiographic examinations and at least one follow-up echocardiographic examination within the first year of the initial examination. The patients were divided into left- and right-sided breast cancer groups to compare the results. The two groups were compared regarding the means of 2D Left Ventricular Ejection Fraction (LVEF), 3D LVEF, Global Longitudinal Strain (GLS), and Global Circumferential Strain (GCS) before and after radiotherapy. Analysis of Covariance (one-way ANCOVA) was used to compare the results ($\alpha = 0.05$). All analyses were carried out using the SPSS software, version 26.

Results: The changes in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS were statistically significant among all the patients irrespective of cancer laterality ($P < 0.001$, $P < 0.001$, $P = 0.001$, and $P = 0.002$, respectively). However, no significant differences were observed between the left- and right-sided breast cancer groups vis-à-vis the means of 2D-LVEF, 3D-LVEF, GLS, and GCS ($P = 0.44$, $P = 0.65$, $P = 0.21$, and $P = 0.25$, respectively).

Conclusions: The study results showed significant declines in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS following radiotherapy. The patients with right-sided breast cancer exhibited a significant decrease in all the mentioned measures, whereas those with left-sided breast cancer showed no significant decline in post-radiotherapy speckle-tracking parameters. In addition, comparison of the patients with left- and right-sided breast cancers revealed no significant difference in the echocardiographic parameters of cardiotoxicity regarding cancer laterality.

**Corresponding author:* Shirin Habibi Khorasani, Cardio-Oncology Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Hashemi Rafsanjani Blvd, Tehran 1995614331, Iran. Cellphone: +98-9131986619, Email: shirin9565.khorasani@gmail.com.

1. Background

Breast cancer is the most common cancer and the second major cause of death amongst females (1, 2). Due to substantial advances in early detection and management, including chemotherapy, breast surgery, radiotherapy, and hormone therapy, more than 90% of patients with breast cancer are expected to survive for longer than five years (3), leading to the growing number of breast cancer survivors who are at risk of developing major toxicities resulting from chemo-radiotherapy (4, 5). Even though changes in cardiac biomarkers can occur earlier, Left Ventricular Ejection Fraction (LVEF) has been considered the gold standard for the detection of chemotherapy-induced cardiotoxicity (6). The amount of LVEF change that is indicative of cardiotoxicity is controversial. However, a minimum 5% decrease in symptomatic patients and a minimum 10% fall in asymptomatic patients to less than 55% is a universally agreed-upon definition (7, 8).

Based on the recent multidisciplinary approach to breast cancer management, radiation therapy is the principal modality to minimize the risk of local recurrence and improve patient survival (9, 10). Nevertheless, several unwanted cardiovascular effects of radiotherapy have been previously described, with Left Ventricular (LV) dysfunction, heart failure, coronary artery disease, myocardial ischemia, valvular disturbances, pericarditis, conduction system disorders, and myocardial fibrosis comprising the major adverse effects (2, 5). The correlation of radiation-induced toxicity with the excessive exposure of the heart to radiation has led to the development of several techniques to reduce its effects, including treatment-field adjustments with computed tomography, prone positioning, and respiratory gating (11).

Breast cancer laterality has been a major concern during radiotherapy. Despite all the hypotheses in favor of an increased risk of cardiotoxicity in patients with left-sided breast cancer, the literature still abounds with substantial controversy in this regard (2, 4, 12, 13). A study on more than 16000 patients with breast cancer found no significant difference between left- and right-sided breast cancers regarding cardiac morbidities (14). Another investigation conducted in 2018 concluded that laterality had no effects on the parameters of radiotherapy-induced cardiotoxicity, including LVEF and N-Terminal pro B-type Natriuretic Peptide (NT-proBNP) (6). Two other recent studies performed in 2020 also showed no morbidity or mortality differences between the women with right- and left-sided breast cancers (15, 16).

2. Objectives

Given that radiotherapy plays a major role in cancer management and that appropriate techniques can significantly reduce its cardiotoxic effects, an understanding of the cardiac effects of radiotherapy based on laterality can be of substantial value. To that end, the present study aims to investigate the echocardiographic markers of radiation-induced cardiotoxicity in right- versus left-sided breast cancer. The results are supposed to help cardiologists and oncologists to opt for the most appropriate management strategies based on individual patients' conditions.

3. Patients and Methods

The study protocol was approved by the Institutional Ethics Committee, and the requirement for informed consent was waived by the institutional review board due to the retrospective nature of the study.

3.1. Data Collection

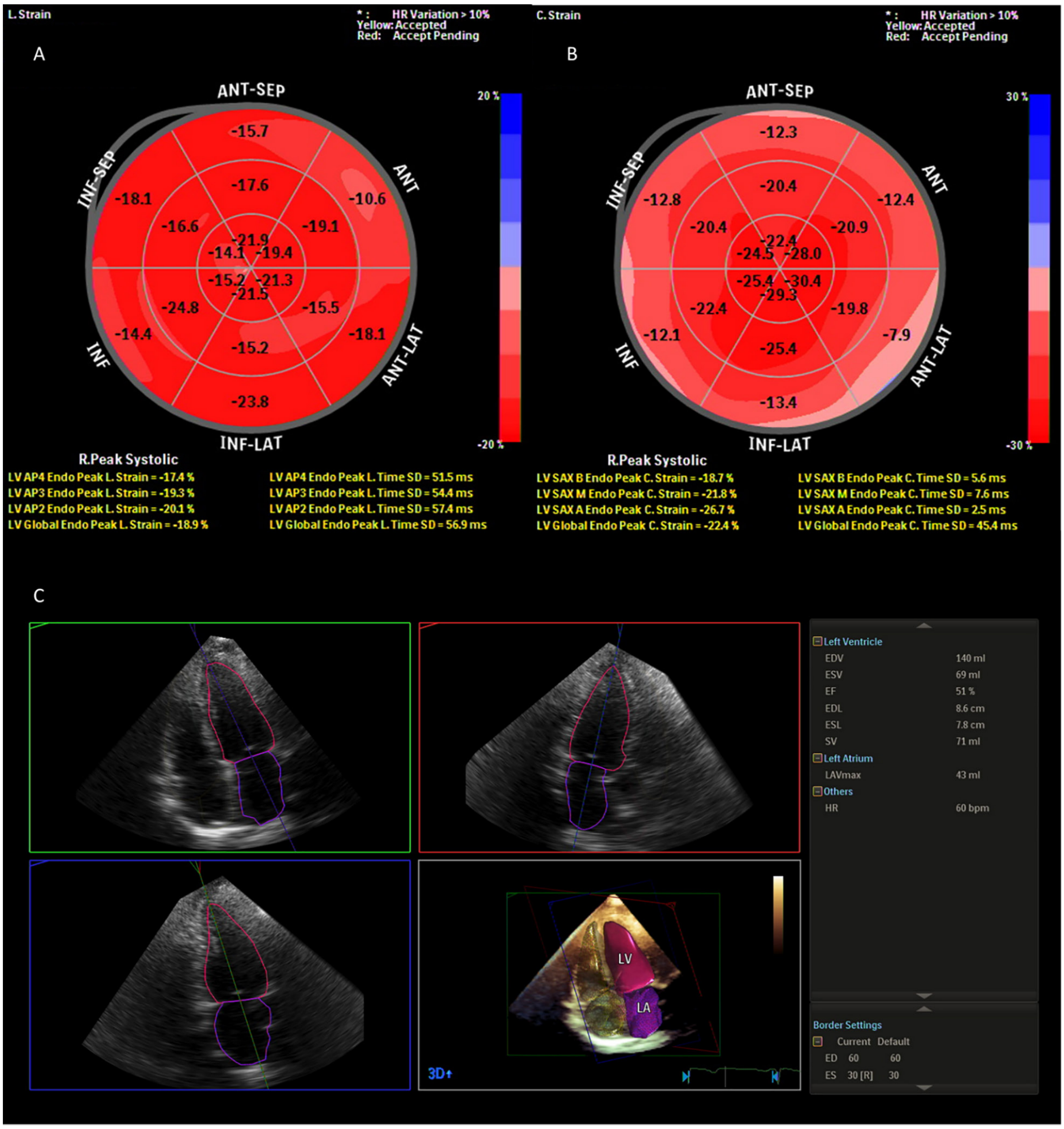
The current investigation reviewed the records of 430 consecutive women with breast cancer who were referred to the Cardio-Oncology Department of Rajaie Cardiovascular Medical and Research Center between April 2017 and September 2020. The exclusion criteria consisted of a previous history of any malignancy, a prior history of radiotherapy for any cause, significant underlying heart diseases such as baseline LVEF < 50%, significant valvular stenosis (more than mild stenosis), significant valvular regurgitation (more than moderate regurgitation), clinical heart failure, and significant coronary artery disease (more than mild stenotic lesions in any coronary artery), no history of pre-radiotherapy echocardiography, and no follow-up echocardiography within the first year of the initial examination. Ultimately, 72 patients with a diagnosis of breast cancer who had baseline echocardiographic examinations together with at least one follow-up echocardiographic examination within the first year of the initial examination were enrolled into the study.

The study population's demographic data, including age, weight, height, Body Mass Index (BMI), family history of malignancy, breast cancer laterality (left- vs right-sided), chemotherapy and radiotherapy status, and interval between the last radiotherapy and echocardiographic examinations, were extracted from the patients' records.

3.2. Image Analysis

Transthoracic echocardiographic examinations were performed by echocardiography fellows in training and were supervised by attending echocardiologists. Global Longitudinal Strain (GLS) and 2D images were acquired using GE Vivid S60 Ultrasound Machine and Philips Affiniti 70 Ultrasound Machine. Additionally, GLS, Global Circumferential Strain (GCS), and 3D images were obtained using Philips Epiq 7c Ultrasound System (Figure 1). Color Doppler echocardiography was utilized to measure mitral and aortic regurgitation. The severity of valvular regurgitation was estimated based on the latest guideline of the American Society of Echocardiography (17). Based on the severity of valvular regurgitation, the patients were divided into five groups; i.e., "no regurgitation", "mild regurgitation", "mild to moderate regurgitation", "moderate regurgitation", and "more than moderate regurgitation". The presence of pericardial effusion was assessed in all acoustic windows. If present, the largest diameter was recorded and the amount of pericardial effusion was categorized as "no effusion", "small effusion", "moderate effusion", and "large effusion" in the absence of pericardial effusion and when the largest diameter of the pericardial effusion was less than 10 mm, between 10 and 20 mm, and greater than 20 mm, respectively. Systolic Pulmonary Artery Pressure (SPAP) was estimated by adding the right atrial pressure to the tricuspid regurgitation gradient based on the simplified

Figure 1. The Average Global Longitudinal Strain, Global Circumferential Strain, and 3D Analysis via Speckle Tracking and the 3D Heart-Model.



(A) Longitudinal strain bull's eye plot in a patient with left-sided breast cancer three months following the last radiotherapy session. A decreased longitudinal strain can be seen in the basal segment (mostly the anterior wall). (B) Circumferential strain bull's eye in the same patient with decreased strain in the basal segment. (C) 3D LVEF analysis in the same patient with the 3D Heart-Model, showing preserved LV systolic function. LV, left ventricle; EF, ejection fraction.

Bernoulli equation (18). Follow-up echocardiography was performed with the same machine used in the baseline examinations. The images were stored on the Picture Archiving and Communication System (PACS) and were then utilized to obtain GLS and GCS off-line. The analyses of the 3D and speckle-tracking images were performed using off-line TOMTEC-ARENA TTA2 software and QLab, version 13.0 (Figure 2).

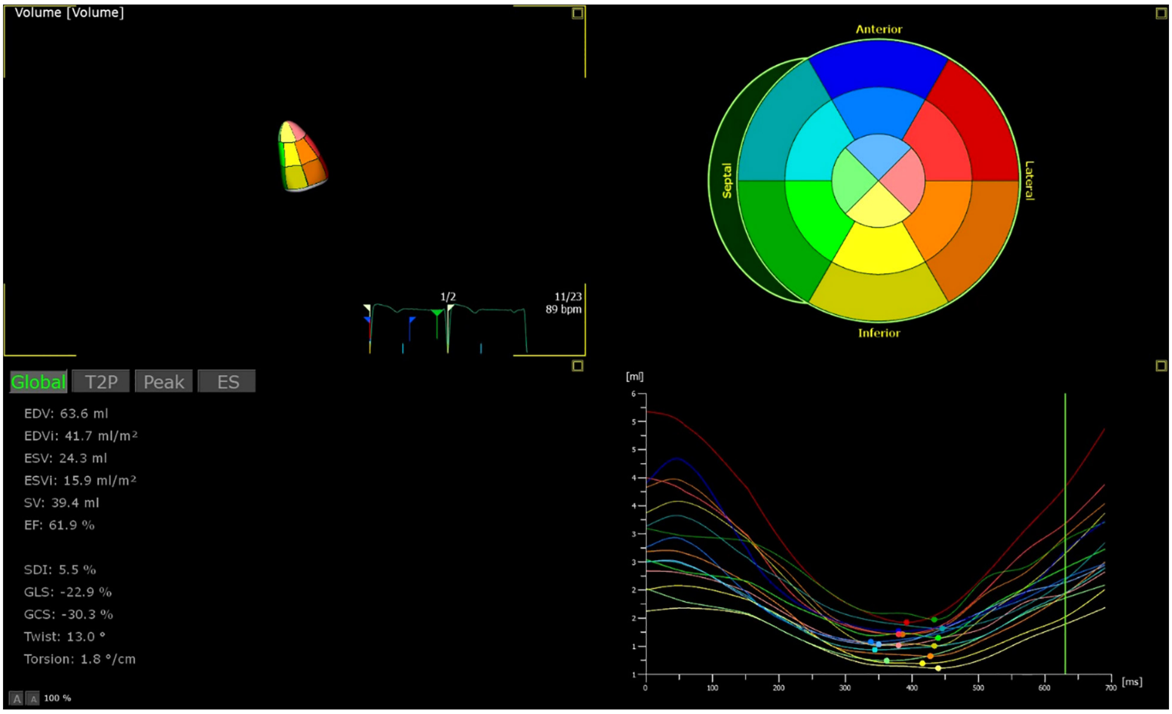
3.3. Data Analysis

The study population's data extracted from the echocardiographic examinations were recorded. Then, the patients were divided into left- and right-sided breast cancer groups to compare the results. It should be noted that these two groups as well as all patients were compared before and after radiotherapy.

3.4. Statistical Analysis

The continuous variables were described as mean ± Standard Deviation (SD) where applicable, while the categorical variables were described as percentages. The assumption of normality was checked using one-sample Kolmogorov–Smirnov test. Differences between the groups at baseline were assessed using Mann–Whitney U test. When a significance level ($P < 0.05$) was identified, Bonferroni post-hoc test was used to identify the differences between the groups and to correct for multiple comparisons. Additionally, Analysis of Covariance (one-way ANCOVA) was performed to adjust for the effects of baseline differences between the study groups ($\alpha = 0.05$). GLS was compared between the subjects through the univariate analysis of variances, and the results were compared between the groups via student t-test. Other variables were analyzed

Figure 2. 3D Image Analysis by TOMTEC Software



Data regarding 3D LVEF and global longitudinal and circumferential strains have been depicted at the bottom left.

using nonparametric tests, including Mann–Whitney U test. IBM® SPSS® Statistics, version 26 was used for data analysis, and p-values less than 0.05 were considered statistically significant.

4. Results

The present study was conducted on 72 consecutive patients with breast cancer under radiation therapy. The study population was divided into two groups based on breast cancer laterality; i.e., right-sided involvement (36/72; 50.0%) and left-sided involvement (36/72; 50.0%). The mean age of the participants was 50.9 ± 10.7 years, and their BMI ranged from 18.9 to 38.7 kg/m2 (28.2 ± 4.8 kg/m2). In addition, two patients (2.8%) had a history of mild coronary artery disease and 39 (54.9%) had the family history of any cancer. Moreover, 71 women (98.6%) underwent chemotherapy, with an average of 7.9 ± 2.9 sessions. Radiation therapy was also performed for all the patients (averagely 27.7 ± 5.1 sessions). Chemo-radiotherapy protocols were all based on the prescription of the patients' oncologists. The calculated interval between the last radiotherapy session and the post-radiotherapy echocardiography (from at least two days to at most 360 days) was less than one month in 23 patients (31.9%), between two and six months in 35 (48.6%), and between six and 12 months in 14 patients (19.4%).

The means of 2D-LVEF and 3D-LVEF before radiotherapy were 53.3 ± 2.9% and 56.1 ± 3.6%, respectively. Following radiotherapy, these values changed to 50.9 ± 3.6% and 52.3 ± 3.4%, respectively. The decline in the means of 2D-LVEF and 3D-LVEF was statistically significant among all the patients irrespective of cancer laterality (P < 0.001 in both) (Table 1).

The absolute values of the average GLS and GCS before radiotherapy were 18.5 ± 2.2% and 25.3 ± 9.3%, respectively. After radiotherapy, these measures changed to 17.3 ± 2.4% and 22.2 ± 9.3%, respectively. The decline in both variables was statistically significant notwithstanding cancer laterality (P = 0.001 and P = 0.002, respectively) (Table 1).

The echocardiographic measures for the patients with right- and left-breast involvement have been listed in Table 2 and Figure 3. In the group of patients with right-sided breast

Table 1. Descriptive Analysis of the 72 Patients with Breast Cancer Assessed before and after Radiation Therapy

	Before Radiotherapy	After Radiotherapy	P-value
Age (y)	50.9 ± 10.7		
BMI (kg/m²)	28.2 ± 4.8		
2D-LVEF (%)	53.3 ± 2.9	50.9 ± 3.6	< 0.001*
3D-LVEF (%)	56.1 ± 3.6	52.3 ± 3.4	< 0.001*
GLS (%)	18.5 ± 2.2	17.3 ± 2.4	0.001*
GCS (%)	25.3 ± 9.3	22.2 ± 9.3	0.002*
SPAP (mmHg)	25.6 ± 6.9	26.5 ± 5.4	0.17

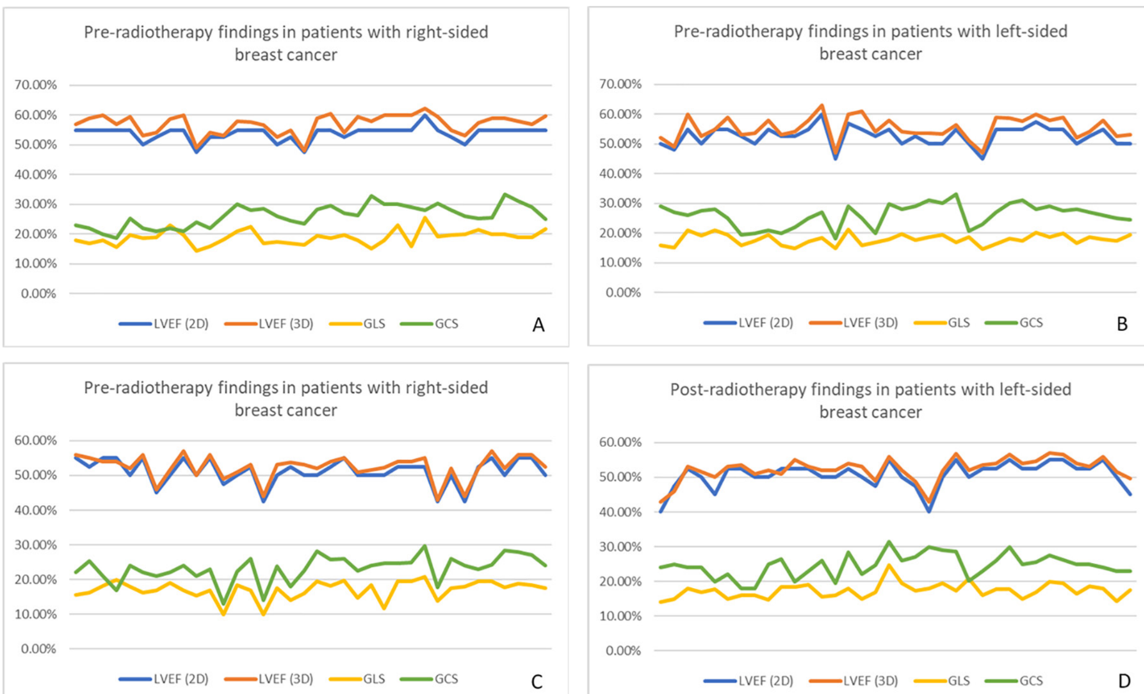
Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain; SPAP, systolic pulmonary artery pressure. Measures for GLS and GCS have been mentioned as absolute values in the table.

Table 2. Descriptive Analysis of the 72 Patients with Breast Cancer Based on Laterality before and after Radiotherapy

	Right Breast Involvement (n = 36)			Left Breast Involvement (n = 36)			Comparison of the Two Study Groups
Variables	**Before radiotherapy**	**After radiotherapy**	**P-value**	**Before radiotherapy**	**After radiotherapy**	**P-value**	**P-value**
2D-LVEF (%)	53.9 ± 2.4	51.1 ± 3.6	< 0.001*	52.7 ± 3.3	50.7 ± 3.7	0.006*	0.44
3D-LVEF (%)	57.0 ± 3.3	52.4 ± 3.5	< 0.001*	55.3 ± 3.8	52.3 ± 3.3	< 0.001*	0.65
GLS (%)	18.9 ± 2.5	17.1 ± 2.7	0.001*	18.0 ± 1.8	17.5 ± 2.1	0.24	0.21
GCS (%)	24.8 ± 11.6	22.7 ± 4.3	0.003*	25.9 ± 4.7	21.5 ± 13.5	0.34	0.25
SPAP (mmHg)	27.1 ± 8.1	27.1 ± 5.6	0.50	24.2 ± 5.2	25.9 ± 5.2	0.21	0.41

Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain; SPAP, systolic pulmonary artery pressure. Each variable was assessed intra- and inter-groups for right- and left-sided breast cancers. Measures for GLS and GCS have been mentioned as absolute values in the table.

Figure 3. Pre- and Post-Radiotherapy Echocardiography Findings in Patients with Right- and Left-Sided Breast Cancers.



The means of GLS and GCS have been depicted as positive values for easier comparison and interpretation. Pre-radiotherapy data have been shown in sections (A) and (B) for right- and left-sided breast cancers, respectively. Post-radiotherapy data have been shown in sections (C) and (D) for right- and left-sided breast cancers, respectively.

cancer, the decrease in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS was statistically significant (P < 0.001, P < 0.001, P < 0.001, and P < 0.003, respectively). In the left-sided breast cancer group, the decline in the means of 2D-LVEF and 3D-LVEF was statistically significant after radiotherapy (P = 0.006 and P = 0.001, respectively). However, this was not the case for the means of GLS and GCS in the group with left-sided breast cancer (P = 0.24 and P = 0.34, respectively).

The results revealed no significant difference between the two study groups (Table 2 and Figure 3) regarding the decline in the means of 2D-LVEF and 3D-LVEF (P = 0.44 and P = 0.65, respectively). The results also showed no significant difference between the two groups concerning the decrease in the absolute values of GLS and GCS (P = 0.21 and P = 0.25, respectively).

In the baseline echocardiographic examination, three patients (4.2%) had moderate mitral regurgitation. The other 69 patients (95.8%) either had no regurgitation or had less than moderate regurgitation. In the post-radiotherapy examination, only one patient (1.4%) developed moderate to severe mitral regurgitation about seven months after the last radiotherapy session. The baseline mitral regurgitation severity was estimated as moderate in her, and she was candidate for medical follow-up regarding LV size, LVEF, and patient's medical condition. The severity of mitral regurgitation in the rest of the patients (98.6%) was not more than moderate in the post-radiotherapy examination (Table 3).

In the pre-radiotherapy examination, only two patients (2.8%) had moderate aortic regurgitation. The rest of the patients (97.2%) had no or less than moderate regurgitation. Following radiation therapy, neither of the abovementioned patients developed more than moderate aortic regurgitation (Table 3).

Prior to radiation therapy, four patients (5.6%) had small pericardial effusion. The post-radiotherapy examination revealed five patients (7.0%) with pericardial effusion (small

Table 3. The Prevalence of Mitral Regurgitation, Aortic Regurgitation, and Pericardial Effusion in the Study Population based on Cancer Laterality

	All Patients with Breast Cancer (n = 72)		Right Breast Involvement (n = 36)		Left Breast Involvement (n = 36)	
Variables	**Before radiotherapy n (%)**	**After radiotherapy n (%)**	**Before radiotherapy n (%)**	**After radiotherapy n (%)**	**Before radiotherapy y n (%)**	**After radiotherapy n (%)**
Mitral regurgitation						
No	5 (6.9%)	1 (1.4%)	3 (8.3%)	0 (0%)	2 (5.5%)	1 (2.8%)
Mild	51 (70.8%)	55 (76.3%)	24 (66.7%)	27 (75.0%)	27 (77.1%)	28 (77.8%)
Mild to moderate	13 (18.1%)	13 (18.1%)	6 (16.7%)	6 (16.7%)	7 (19.4%)	7 (19.4%)
Moderate	3 (4.2%)	2 (2.8%)	3 (8.3%)	2 (5.5%)	0 (0%)	0 (0%)
More than moderate	0 (0%)	1 (1.4%)	0 (0%)	1 (2.8%)	0 (0%)	0 (0%)
Aortic regurgitation						
No	49 (68.0%)	44 (61.1%)	24 (66.7%)	21 (58.4%)	25 (69.4%)	23 (63.9%)
Mild	18 (25.0%)	20 (27.8%)	8 (22.2%)	9 (25.0%)	10 (27.8%)	11 (30.5%)
Mild to moderate	3 (4.2%)	6 (8.3%)	2 (5.5%)	4 (11.1%)	1 (2.8%)	2 (5.5%)
Moderate	2 (2.8%)	2 (2.8%)	2 (5.5%)	2 (5.5%)	0 (0%)	0 (0%)
More than moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pericardial effusion						
No	68 (94.4%)	67 (93.0%)	35 (97.2%)	34 (94.4%)	33 (91.7%)	33 (91.7%)
Small	4 (5.6%)	4 (5.6%)	1 (2.8%)	1 (2.8%)	3 (8.3%)	3 (8.3%)
Moderate	0 (0%)	1 (1.4%)	0 (0%)	1 (2.8%)	0 (0%)	0 (0%)
Large	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

in four and moderate in one). There was no case of large or hemodynamically significant pericardial effusion during the follow-up (Table 3).

The mean SPAP was 25.6 ± 6.9 mmHg at baseline, which changed to 26.5 ± 5.4 mmHg in the post-radiotherapy examination (Table 1). The change in the mean SPAP was not statistically significant in the entire study population and in those with right- or left-sided breast cancer ($P = 0.17$, $P = 0.50$, and $P = 0.21$, respectively). Furthermore, no significant difference was observed between the two groups regarding the change in the mean SPAP ($P = 0.41$) (Table 2). In the post-radiotherapy examination, only two patients (2.8%) had the SPAP of more than 40 mmHg. One of these patients had right-sided breast cancer with moderate-to-severe mitral regurgitation, and her pulmonary hypertension (SPAP = 50 mmHg) was attributed to increased left atrial pressure. The other patient had left-sided breast involvement, with an increase in SPAP from 17 mmHg to 40 mmHg following radiotherapy.

5. Discussion

The present study aimed to evaluate cardiotoxicity in patients suffering from breast cancer under radiation therapy. The findings revealed a statistically significant decline in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS among the patients following radiotherapy, which was prominent in those with right-sided breast cancer. The results of subgroup analysis also demonstrated that the decrease in the means of GLS and GCS was not statistically significant in the group with left-sided breast cancer. Nonetheless, based on the clinical criteria, there was no significant difference between the groups of patients with right- and left-sided breast cancers with respect to cardiotoxicity.

The present study results revealed an approximately 2.4% decline in the mean 2D-LVEF and a 3.8% fall in the mean 3D-LVEF after radiotherapy, which was statistically significant ($P < 0.001$ in both left- and right-sided groups). According to the commonly used definition of cardiotoxicity,8 the mean change in LVEF was less than 5% in the patients and was thus not clinically significant. In 2017, Bian et al. (19) found a 3.0% LVEF decrement in patients undergoing concurrent chemotherapy and irradiation, which was attributed mainly to doxorubicin, but not to radiotherapy. Sayan et al. (20) also evaluated 141 patients under chemo-radiotherapy and found a 2 - 4% decline in LVEF. They reported that the rate of the symptomatic LVEF decline was similar between conventional and hypofractionated radiation therapies.

In the current study, the drop in the means of GLS and GCS was statistically significant; the former showed a 1.2% decrease ($P = 0.001$) and the latter a 3.1% decline ($P = 0.002$). In 2019, Anthony et al. (21) demonstrated no significant difference between the post- and pre-radiotherapy echocardiographic assessments concerning GLS, GCS, and global radial strain. Their results were consistent at a six-month follow-up. They reported a significant decline in strain parameters following chemotherapy; nevertheless, they obtained no similar results in the comparison of pre- and post-radiotherapy measures. The sample size of their study was smaller compared to the present investigation, which might be the probable reason for the dissimilarity between the findings. Additionally, different radiation therapy protocols in various centers and wide ranges of protective medical treatments might have resulted in this discrepancy.

In the present research, the results of subgroup analysis indicated a statistically significant decline in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS in the patients with right-sided breast involvement, while no similar results were obtained regarding the means of GLS and GCS in those with left-sided breast cancer. Comparisons of the right- and left-sided breast cancers also revealed no significant differences in terms of the decline in any echocardiographic parameter before and after radiotherapy. The literature contains substantial controversy surrounding radiation therapy-induced cardiotoxicity and breast cancer laterality. Several studies on the markers of cardiotoxicity have failed to demonstrate significant differences between left- and right-sided breast cancers (1, 6, 19). Recent investigations on cardiac morbidity and mortality following radiotherapy have also found no differences between women with left- and right-sided breast cancers (5, 14). On the other hand, Zaher et al. (2) in 2018 and Nack et al. (12) in 2019 reported a significantly greater LVEF decline and myocardial dysfunction in patients with left-sided breast cancer and assigned this finding to a higher radiation dose delivered to the heart in these patients. Correa et al. (9) and Boero et al. (11) reported lower survival and increased cardiac morbidities in patients with left-sided involvement, which were attributed to a higher incidence of coronary artery damage in these patients, but not to direct myocardial toxicity. The present researchers assumed that this finding might be relevant to the baseline characteristics of the patients with right-sided involvement. However, it did not reach statistical significance. In 2020, Andersen et al.16 showed a greater LVEF decline in patients with right-sided breast cancer. Their results, albeit non-significant, showed more consistency with the current study findings. Andersen and colleagues also concluded that despite advances in novel radiation techniques, myocardial dysfunction might be a notable matter of concern in patients with right-sided breast cancer similar to those with left-sided involvement.

The present study results demonstrated that the prevalence of significant valvular regurgitation; i.e., more than moderate mitral and aortic regurgitation, was not substantial. In 2020, Xu et al. (22) detected a significantly increased risk for the development of valvular insufficiency following radiotherapy and stated that this complication was late-onset and evident in those who had undergone radiation therapy more than two decades earlier. In the current research, the patients were evaluated during the first year following radiotherapy, and the absence of significant valvular involvement was rational.

In the present study, post-radiotherapy pericardial effusion was evident in 7% of the patients, the majority of whom (75%) had left-sided breast cancer (Table 3). In a previous study on breast cancer, 175 patients were followed for a median of 4.7 years. The prevalence of pericardial effusion was 5.7% in those patients, with the rate being higher among those with left-sided involvement (6, 23). These findings were in agreement with those of the current investigation, even though this study lacked a long follow-up, indicating the higher exposure of the pericardium in left-sided radiotherapy.

In the current evaluation of 72 women with breast cancer, increased PAP (SPAP > 40 mmHg) was reported in only two patients, one of whom had moderate-to-severe mitral regurgitation with elevated left atrial pressure. To our knowledge, there is no recent comprehensive study on the effect of breast radiotherapy on PAP. In 1999, Gustavsson et al. (23) assessed late cardiac effects after adjuvant radiotherapy in premenopausal patients and observed normal SPAP in the whole study population. Their findings, albeit inadequate, were concordant with those of the current research and could be a matter of concern for the future research.

The present study had several limitations. The cardio-oncology department under investigation is a referral center for patients with cancer who may be visited in the middle of their treatment course. Consequently, the researchers had some difficulties collecting pre-radiotherapy information from patients since some of them had no available echocardiographic images for analysis. Moreover, the COVID-19 outbreak led to unwanted delays in treatments, changes in management plans, and non-referrals for follow-up visits. In addition, the researchers were required to adhere to the World Health Organization's guidelines on minimizing non-emergent procedures during the outbreak. Another drawback of note was that concurrent chemotherapy, a major component of the patients' treatment plans, might have exerted some additional effects on the study results.

In conclusion, the present study results revealed a significant decline in the means of 2D-LVEF, 3D-LVEF, GLS, and GCS among the patients with breast cancer following radiotherapy. However, there were no significant differences between the left- and right-sided breast cancers with respect to the echocardiographic parameters of cardiotoxicity regarding cancer laterality. The results suggested that patients with right-sided breast cancers should be provided with similar close surveillance and concern to those with left-sided involvement.

5.1. Ethical Approval

Ethical Considerations The study design and protocols were approved by the Ethics Committee of the Research Deputyship in Rajaie Cardiovascular, Medical, and Research Center (ID: IR.RHC.REC.1399.037). Obtaining informed consents was waived due to the retrospective nature of the study.

5.5. Informed Consent

This was a retrospective study and regarding the journal guideline, obtaining informed consents was not needed.

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Authors' Contribution

Study concept and design: A.A.; acquisition of data: S.H.K., S.A.E., S.A.M., R.A., P.A., and H.K.; analysis and interpretation of data: S.H.K. and K.M.; drafting of the manuscript: S.H.K.; critical revision of the manuscript for important intellectual content: M.M. and F.N.; statistical analysis: S.A. and B.G.

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