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Impact of Three-Dimensional Conformal Radiotherapy Boost Techniques on Cardiac Toxicity in Left-Sided Breast Cancer Patients

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ABSTRACT

Background: Radiotherapy (RT) for left breast cancer poses a significant hazard of cardiac damage, despite advancements in three-dimensional conformal radiotherapy (3D-CRT). Identifying correlations between dosimetric parameters and markers of cardiac dysfunction is critical for optimizing treatment planning.

Objectives: This study aimed to evaluate the impact of 3D-CRT boost techniques on cardiac toxicity, focusing on correlations between dosimetric parameters, cardiac biomarker and echocardiographic measurements.

Patients and methods: We conducted a prospective study involving 50 females with left breast cancer receiving postoperative RT at Qena University Hospital. Dosimetric parameters, including mean cardiac dose and LV volume exposed to ≥ 30 Gy (V30) were calculated. Biomarkers [Brain Natriuretic Peptide (BNP)] and echocardiographic markers [Ejection Fraction (EF) and Global Longitudinal Strain (GLS)] were analyzed pre-radiotherapy, and at one and six months post-radiotherapy.

Results: The average cardiac dose was 6.1 ± 3.2 Gy, and the average V30 was 8.2 ± 3.4%. BNP levels increased significantly post-RT ($p < 0.001$), while EF and GLS showed marked declines ($p < 0.05$). Significant statistical correlations were observed between V30 and GLS ($r = -0.4490$, $p = 0.0011$).

Conclusion: RT for left-sided breast cancer increases cardiac toxicity. Correlations between V30 and cardiac dysfunction underscore the need for enhanced dose-sparing techniques to minimize long-term risks. Future strategies should integrate advanced modalities like deep inspiration breath-hold (DIBH) and proton therapy.

Keywords: Radiotherapy boost, 3D-CRT, Cardiac toxicity, Breast cancer, V30.

INTRODUCTION

Radiotherapy (RT) is a cornerstone in the treatment of breast cancer, particularly after breast-conserving surgery (BCS). It considerably decreases local relapse rates, with a relative risk reduction of 70–88%, and improves long-term survival [1, 2]. However, RT for left-sided breast cancer inadvertently exposes the heart to radiation, causing higher risk of radiation-induced heart disease (RIHD) [3, 4].

Historically, older RT techniques resulted in significant cardiac mortality, with elevated doses to heart structures such as the left ventricle (LV) [5]. Advancements in three-dimensional conformal radiotherapy (3D-CRT) have considerably lowered cardiac radiation exposure, with the mean heart dose dropping from 13.3 Gy in the 1970s to 2.3 Gy by 2006. Despite these improvements, high-dose regions, such as areas of the heart receiving ≥ 30 Gy (V30), remain a concern [6, 7, 8].

Cardiac biomarkers, especially Brain Natriuretic Peptide (BNP), and imaging parameters, especially global longitudinal strain (GLS) and ejection fraction (EF), have emerged as sensitive tools for detecting subclinical myocardial dysfunction. GLS, in particular, provides an early indication of myocardial injury, often preceding changes in EF [9, 10].

This study evaluates the impact of 3D-CRT boost techniques on cardiotoxicity in patients with left breast cancer. By analysing correlations between dosimetric parameters, cardiac biomarkers, and echocardiographic findings, the study aims to underscore the importance of cardiac-sparing strategies during RT planning.

PATIENTS AND METHODS

Study design and participants: This prospective study has been carried out at the Clinical Oncology and Cardiology Departments, Qena University Hospital, Egypt. The study included 50 women aged > 30 years with pathologically confirmed left-sided breast cancer requiring postoperative RT. Patients with age < 30 years , lacking indication for RT, prior RT, LVEF < 55 %, poor echocardiographic imaging quality, severe systemic illness, ACS, significant valvular heart disease, atrial fibrillation or significant arrhythmia were excluded.

Radiotherapy protocol: Patients received RT using 6 MV photon beams delivered by a 3D linear accelerator (Elekta Precise). A full dosage of 42.72 Gy was administered in 23 fractions to the thoracic wall and regional lymph nodes. The mean cardiac dose and LV V30 (volume of the left ventricle receiving ≥ 30 Gy) were calculated using the XIO treatment planning system.

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Outcome measures: In addition to detailed history and clinical examination:

1. Echocardiography: Echocardiographic assessment via GE Vivid E95 (GE Healthcare, USA) was performed to measure left ventricular ejection fraction (LVEF %) (Using biplane Simpson method) and Global Longitudinal Strain (GLS %) (Using speckle tracking echocardiography) at baseline (pre-RT), one month, and six months post-RT. All echocardiographic studies were achieved by two independent observers to minimize inter-observer variability, agreeing to the justifications of American society of echocardiography (ASE) [10].

2. Biomarkers: Plasma BNP levels were measured at baseline (pre-RT), one month, and six months post-RT. Blood samples were collected in EDTA tubes, centrifuged, and the plasma is analyzed using ELISA (Enzyme-Linked Immunosorbent Assay) kits in duplicate with quality control to ensure accuracy.

Ethical approval: Following approval by the Ethical Board of The Faculty of Medicine, South Valley University (Ethical approval code: SVU/MED/ONM027/1/21/1/116). Informed written consent was attained from all participants. The research protocol followed the ethical rules of the 1975 Declaration of Helsinki. Measures were implemented to ensure participants' privacy and data confidentiality, including: Allowing patients the option to decline participation in the study without any consequences. Assigning code numbers to each participant, with their names and addresses securely stored in a separate file. Ensuring patient names were not disclosed during the research process. Using the study results strictly for scientific purposes and not for any other objectives.

Statistical analysis

All data were assembled, arranged and statistically evaluated using SPSS 27.0 for windows (SPSS Inc., Chicago, IL, USA). Data were verified for normal distribution by means of the Shapiro Walk test. Qualitative data were characterized as frequencies and relative percentages. Quantitative data were stated as mean ± SD (Standard deviation) and range. Group comparisons were conducted using repeated-measures ANOVA. Pearson's correlation was used to evaluate associations between dosimetric parameters and cardiac outcomes. P value ≤ 0.05 was approved statistically significant.

RESULTS

***Study Population Characteristics*:**

A total of 50 ladies with average age of 48.5 ± 12.5 years. Table (1) showed that six (12%) patients were known to be hypertensive, five (10%) were known to be diabetic, five (10%) had dyslipidemia, and five (10%) were morbidly obese, seven (14%) had a family history of coronary ischemia and none were smokers. The mean BMI was 34.2 ± 5 kg/m².

Table (1): The Patients Baseline Demographic and Clinical Characteristics (N=50)

	Frequency	Percentage	Mean ± SD	Range
Age (years)			48.5 ± 12.5	31 – 70
Less than 40	18	36		
41 – 60	18	36		
More than 60	14	28		
BMI (kg/m^2)			34.2 ± 5	26 – 47
Overweight	12	24		
Obesity Grade I	18	36		
Obesity Grade II	15	30		
Obesity Grade III	5	10		
Menopausal State				
Premenopausal	18	36		
Menopausal	32	64		
Cardiac Risk Factors				
HTN	6	12		
DM	5	10		
Dyslipidemia	5	10		
Morbid Obesity	5	10		
Family History of CAD	7	14		
Smoking	0	0		

Notes: Continuous data represented as mean ± SD, categorical data in the form of frequency and percentage. **Abbreviations:** BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; SD: Standard deviation.

The tumor characteristics summarized in table (2) and revealed that 80% had invasive ductal carcinoma, and 58% were T1 stage. The majority of tumors were positive for both estrogen receptors (ER) and progesterone receptors (PR) representing 48%. According to TNM classification system, the majority of tumors were classified as T1N0M0. Regarding Ki67 activity, 26 (52%) patients showed low activity, while 24 (48%) showed high activity. The table summarizes the descriptive characteristics of the irradiated breast tumors, including mammographic size, histological types, histological grading, TNM staging, hormonal receptor status, and Ki67.

Table (2): Tumor Characteristics (N = 50)

	Frequency	Percentage
Mammography		
Less than 1 cm	11	22
1 – 2 cm	20	40
2 – 3 cm	10	20
More than 3 cm	9	18
Histological Type		
IDC	40	80
ILC	5	10
MCa	2	4
TCa	3	6
Histological Grading		
Grade I	33	66
Grade II	15	30
Grade III	2	4
TNM Staging		
T1	29	58
T2	16	32
T3	5	10
T4	0	0
N0	42	84
N1	8	16
M0	50	100
M1	0	0
Hormonal Receptor		
ER-PR Negative	12	24
ER-PR Positive	24	48
ER Positive-PR negative	8	16
PR Positive-ER negative	6	12
Ki67		
Low	26	52
High	24	48

Abbreviations: ER: estrogen receptor; PR: progesterone receptor; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; MCa: medullary carcinoma; TCa: tubular carcinoma.

Dosimetric parameters

- The mean cardiac dose was 6.1 ± 3.2 Gy (range: 1.4–11.9 Gy), and the mean LV V30 was 8.2 ± 3.4% (range: 2.4–15%).

Cardiac outcomes: Effect of RT on BNP levels and cardiac function was summarized in table (3) & selected case in figure (1).

- **BNP Levels:** BNP levels significantly increased from 24.8 ± 16.5 pg/mL pre-RT to 42.4 ± 16.6 pg/mL at 1 month post-RT, and further increased to 48.1 ± 16.8 pg/mL at 6 months post-RT ($P < 0.001$) (Figure 2).

  A substantial positive correlation was noticed between BNP levels and V30 and irradiation dose (Pearson test, $P < 0.001$) (Figure 3).
- **Ejection fraction (EF):** EF decreased significantly from 66% ± 7.7% pre-RT to 58% ± 8.3% at 6 months post-RT ($P < 0.001$) (Figure 4).
- **Global longitudinal strain (GLS):** GLS declined from -18.8% ± 1.5% pre-RT to -16.8% ± 0.4% at 6 months post-RT ($P = 0.041$) (Figure 5). A statistically significant negative correlation was found between GLS and V30 at 6-month follow-up (Pearson test, $r = -0.4490$, $P = 0.0011$) (Figure 6).

These findings highlight that radiotherapy (RT) for left breast cancer significantly increased the danger of cardiac toxicity, as evidenced by dose-dependent changes in BNP levels, ejection fraction (EF), and global strain (GLS). Our study confirmed that even with the usage of 3D conformal radiotherapy (3D-CRT), radiation exposure to the heart, particularly in high-dose regions such as the left ventricle (LV), remains a critical factor contributing to myocardial dysfunction.

Table (3): Effect of RT on BNP Levels and Cardiac Function (N = 50)

	Pre-RT	**1-month Post-RT**	**6-month Post-RT**	***P* value***
BNP, pg/ml	24.8 ± 16.5	42.4 ± 16.6	48.1 ± 16.8	< 0.001
EF (%)	66 ± 7.7	65 ± 6.2	58 ± 8.3	< 0.001
GLS (%)	-18.8 ± 1.5	-17.1 ± 0.6	-16.8 ± 0.4	.041

* Repeated Measure ANOVA (comparison between pre-RT, 1-month post-RT, and 6-month post-RT). Significant P-value < 0.05. BNP: brain natriuretic peptide; EF: ejection fraction; LV: left ventricle; GLS: Global Longitudinal Strain.

This figure illustrated the changes in Global Longitudinal Strain (GLS %) at three times.

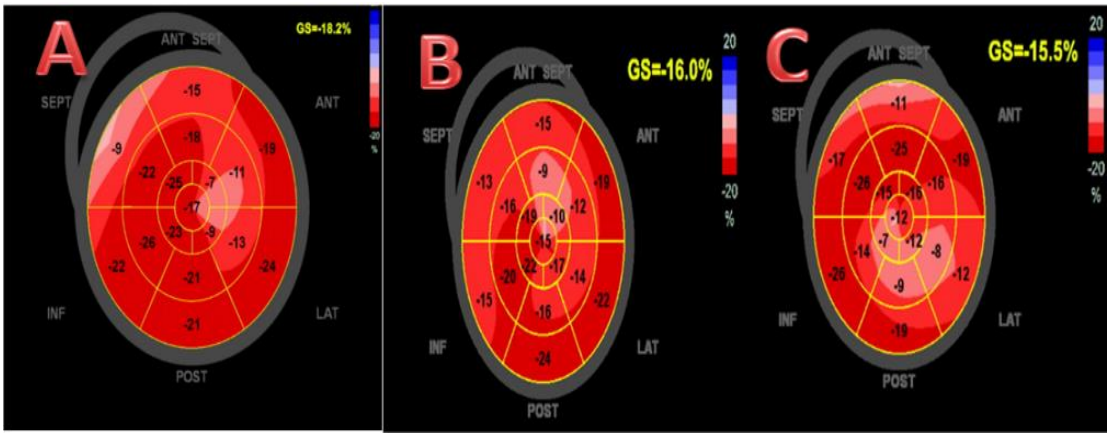

Figure (1): Selected case showing changes in GLS (%) pre- and post-radiotherapy, **A;** pre-radiotherapy (GLS = -18.2 %), **B;** one-month post-radiotherapy (GLS =-16 %), and **C;** six months post-radiotherapy (GLS = -15.5 %).

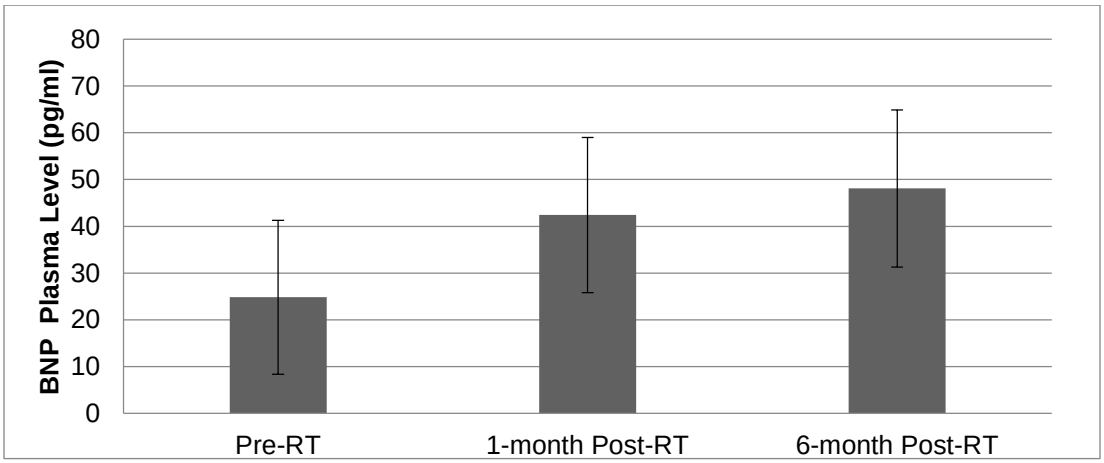

Figure (2): This figure illustrated the changes in brain natriuretic peptide (BNP) levels at three time points: Pre-radiotherapy (Pre-RT), one month post-radiotherapy (1-month Post-RT), and six months post-radiotherapy (6-month Post-RT). BNP levels were significantly increased ($p < 0.001$).

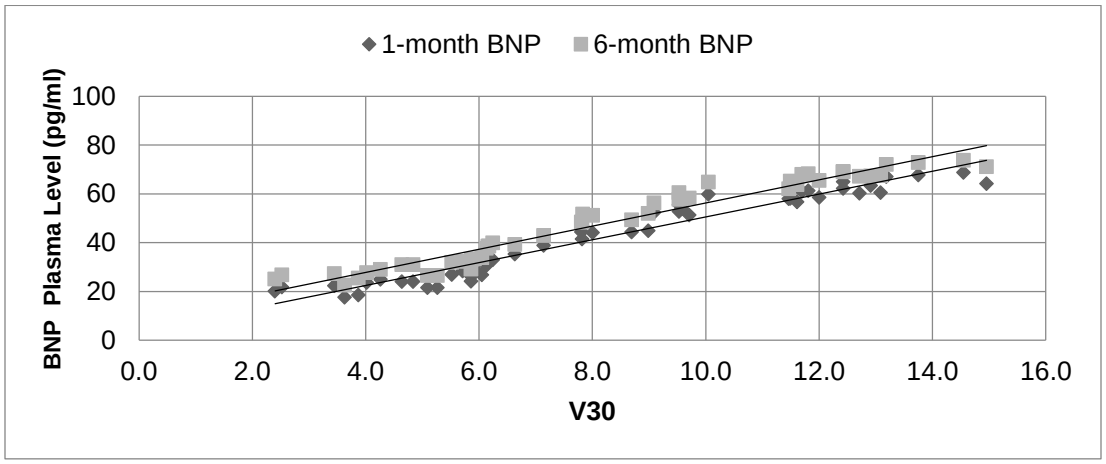

Figure (3): This figure demonstrated a significant positive correlation between V30 and BNP levels at both one-month and six-month follow-ups (Pearson test, $p < 0.001$) indicating that higher radiation doses to the heart are associated with increased BNP levels.

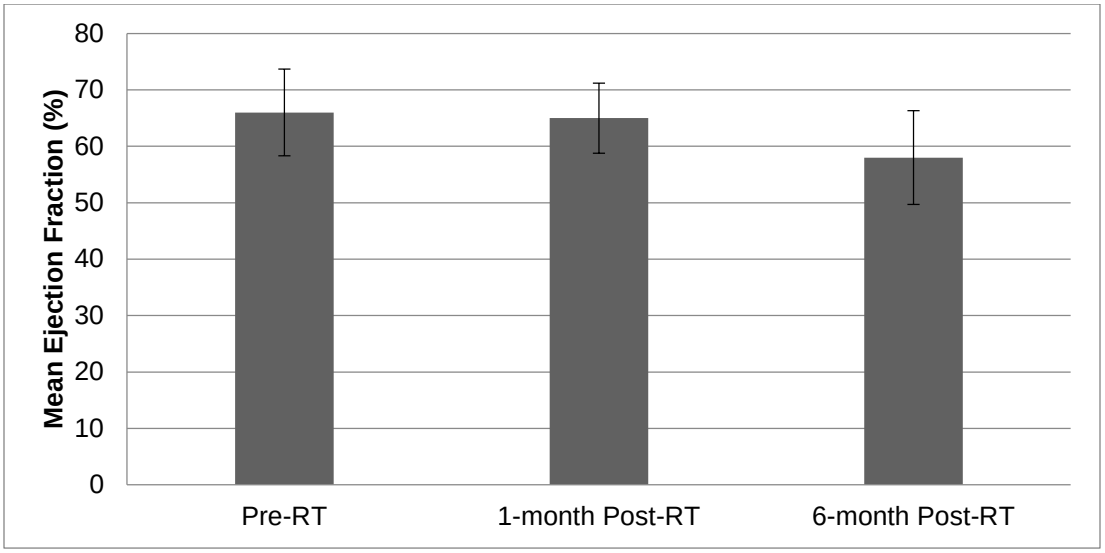

Figure (4): This figure showed the significant decrease in left ventricular ejection fraction (EF) from pre-RT (66% ± 7.7%) to six months post-RT (58% ± 8.3%, $p < 0.001$). The decline in EF post-treatment indicated a significant loss of myocardial function associated with radiation exposure.

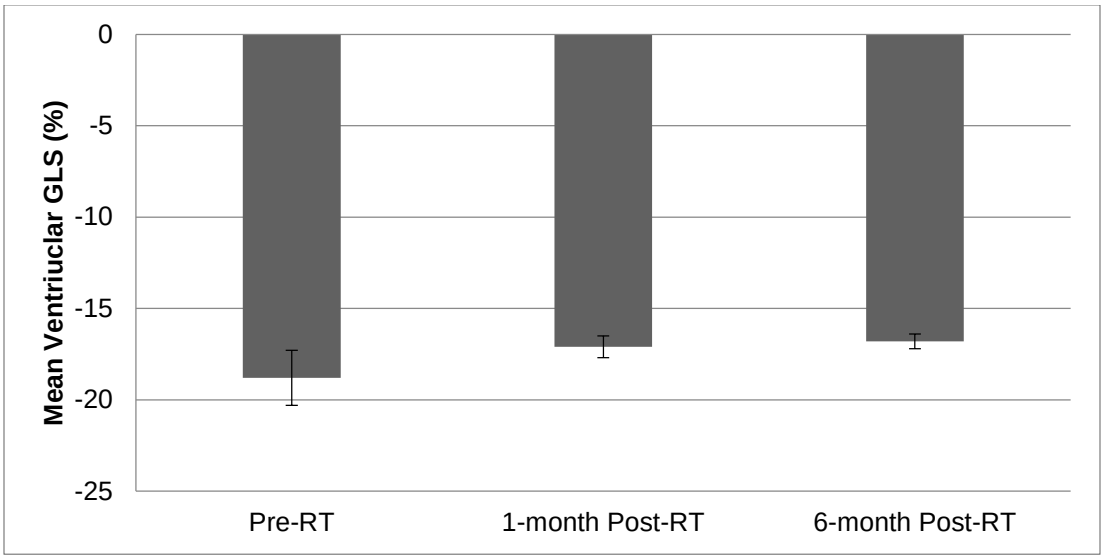

Figure (5): This figure illustrated the decline in Global Longitudinal Strain (GLS) from pre-RT (-18.8% ± 1.5%) to six months post-RT (-16.8% ± 0.4%, $p = 0.041$). The decrease in GLS further supported the finding of subclinical cardiac dysfunction following RT.

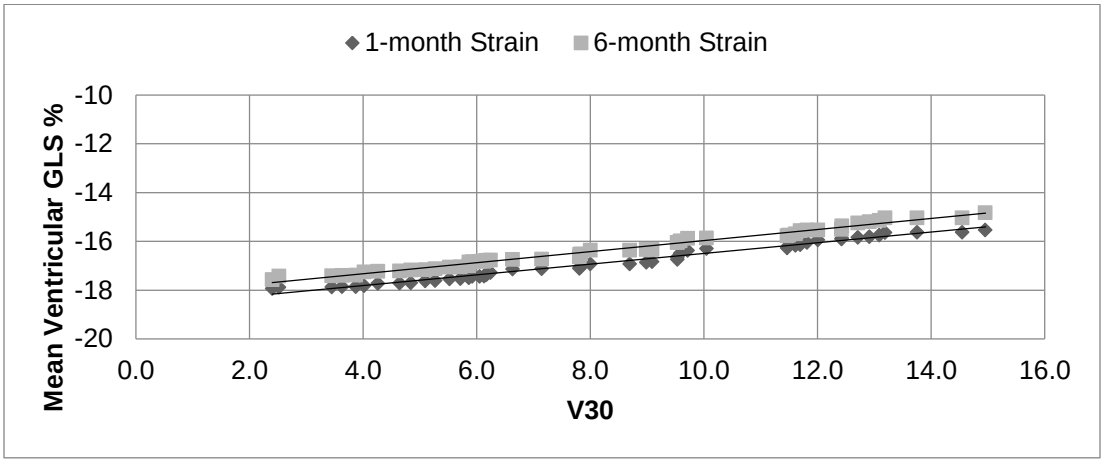

Figure (6): This figure showed the strong negative correlation between V30 and GLS at six months post-RT (r = -0.4490, P = 0.0011). The data indicated that higher radiation doses to the heart were associated with a greater reduction in GLS, a more sensitive marker for early myocardial dysfunction.

DISCUSSION

This study demonstrated the significant cardiac damage related to radiotherapy (RT) for left breast cancer, even with modern 3D-conformal radiotherapy (3D-CRT) techniques. The findings highlighted a dose-dependent relationship between radiation exposure, biomarkers of cardiac injury (BNP), and echocardiographic parameters (EF and GLS). This study focused on the critical role of biomarkers and imaging techniques in detecting subclinical cardiac toxicity due to radiotherapy (RT) in left-sided breast cancer patients

Cardiac dose and toxicity: In this cohort, the mean cardiac dose was 6.1 ± 3.2 Gy, and the mean left ventricular (LV) V30 was 8.2 ± 3.4%. These results are concordant with preceding research, which have demonstrated that radiation exposure to the heart remains a significant concern even with modern RT techniques. For instance, **Taylor *et al.*** [4] observed a reduction in the mean heart dose over the years, from 13.3 Gy in the 1970s to 2.3 Gy by 2006. However, our results align with more recent reports where mean cardiac doses still range between 2–7 Gy in 3D-CRT setups as noticed by **Darby *et al.*** [2] and **Piroth *et al.*** [11]. Despite improvements in RT planning, studies have shown that higher doses, particularly to the LV, can still lead to significant declines in cardiac function. Our results support these findings, as we observed a significant decline in both EF and GLS, which are sensitive markers of myocardial dysfunction.

Our findings underscored that while 3D-CRT reduces heart exposure compared to older techniques, higher V30 values remain a significant predictor of cardiac toxicity. Studies by **Goldoost *et al.*** [7] and **Tuohinen *et al.*** [12] similarly found that an increased volume of the heart receiving ≥ 30 Gy (V30) correlates with greater declines in ejection fraction (EF) and global longitudinal strain (GLS). These parameters highlight the persistent risk of radiotherapy-induced heart disease (RIHD), even with modern protocols.

Biomarkers and cardiac injury: Elevated BNP levels post-RT were a prominent finding in this study. BNP, a marker of ventricular wall stress, has been increasingly recognized as a sensitive early indicator of RT-induced cardiac dysfunction. Our results align with **D'Errico *et al***. [6] and **Palumbo *et al.*** [8], who found similar increases in BNP levels in breast cancer patients after RT. BNP serves as an essential biomarker for early detection of radiation-induced heart disease (RIHD), as it correlates strongly with the radiation dose received by the heart, especially in high-dose regions like V30.

Interestingly, while EF showed a significant decrease from 66% to 58%, GLS proved to be a more sensitive marker for detecting subclinical cardiac dysfunction. Our findings are consistent with **Tuohinen *et al.*** [12], who reported similar declines in GLS in patients who underwent RT for breast cancer. GLS can detect myocardial dysfunction even before changes in EF occur, making it a valuable tool for monitoring subclinical cardiac injury. The significant negative correlation between GLS and V30 in our study underscored the significance of limiting radioactivity

exposure to the heart, particularly in the LV and this also is consistent with findings by **Walker *et al.*** [13] and **Zhang *et al.*** [14].

LIMITATIONS: Small sample size, short follow-up, absence of control group and being single-center study limit the study's generalizability and statistical power. While 3D-CRT remains a widely used technique, it is not without limitations in terms of cardiac sparing. Innovative procedures such as intensity-modulated radiotherapy (IMRT) and proton therapy have demonstrated superior capabilities in reducing heart exposure. IMRT has been displayed to decrease the mean heart dose by approximately 50% compared to 3D-CRT, significantly lowering the risk of cardiac events [15]. Proton therapy offers even greater heart-sparing potential, with mean heart doses often below 1 Gy, thus further minimizing the risk of radiation-induced cardiac damage [16].

Our study supports the need for personalized treatment planning to minimize radiation exposure, especially in the left-sided breast cancer cohort. Incorporating techniques like deep inspiration breath-hold (DIBH) in 3D-CRT protocols can further reduce cardiac toxicity, as shown in studies like that of **Falco *et al.*** [17] who reported a mean heart dose as low as 2–3 Gy with DIBH. Future studies comparing 3D-CRT, IMRT, and proton therapy in terms of long-term cardiac outcomes would provide valuable insights into the most effective RT techniques for minimizing cardiac risk**.**

Clinical implications and future directions:

The clinical implications of our findings are significant. Patients with left-sided breast cancer are at an increased risk of developing radiation-induced heart disease, particularly those receiving higher radiation doses to the LV. By incorporating cardiac-sparing techniques, such as IMRT, proton therapy, and DIBH, clinicians can reduce the risk of long-term cardiac morbidity. Furthermore, regular monitoring of biomarkers like BNP and imaging techniques like GLS can enhance early detection of myocardial injury, allowing for timely interventions to mitigate further damage.

Future research should focus on the following:

1. Longer follow-up: To assess the progression of subclinical cardiac dysfunction to symptomatic disease, enabling better understanding of the long-term effects of RT.
2. Comparative control studies: Evaluating the cardiac outcomes of 3D-CRT, IMRT, and proton therapy to identify the optimal treatment for minimizing radiation-induced cardiac damage.
3. Predictive models: Developing models that integrate dosimetric, biomarker, and echocardiographic data to predict and mitigate cardiac risks during RT for breast cancer.
4. Multicenter study with larger sample size to improve external and statistical validity.

CONCLUSION

Radiotherapy for left-sided breast cancer increases the risk of cardiac toxicity, as shown by dose-dependent changes in BNP, ejection fraction, and global longitudinal strain. Despite using 3D-CRT, radiation exposure to high-dose heart regions, particularly the left ventricle, contributes to myocardial dysfunction. Advanced cardiac-sparing techniques like IMRT, proton therapy, and DIBH can significantly reduce cardiac exposure and should be prioritized in treatment planning. Routine monitoring of cardiac biomarkers and imaging is essential for early detection of cardiac dysfunction. Future studies should focus on long-term follow-up, technique comparisons, predictive models and larger sample size to enhance patient outcomes.

ABBREVIATIONS

- **BNP:** Brain Natriuretic Peptide
- **GLS:** Global Longitudinal Strain.
- **EF:** Ejection Fraction.
- **RT:** Radiotherapy
- **3D-CRT:** Three-Dimensional Conformal Radiotherapy
- **IMRT:** Intensity-Modulated Radiotherapy.
- **DIBH:** Deep Inspiration Breath-Hold
- **CAD:** Coronary Artery Disease
- **ACS:** Acute coronary syndrome

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