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Assessment of early radiation-induced changes in LV function by myocardial strain imaging after breast radiation therapy

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Abstract

Background: Radiation therapy (RT)-induced cardiotoxicity is among the concerning sequelae of breast cancer (BCA) treatment, particularly in HER2-positive breast cancer patients who receive anthracyclines and trastuzumab-based therapy. The aim of this study was to assess for early RT-induced changes in echocardiographic and circulating biomarkers of left ventricular (LV) function and evaluate their association with radiation dose to the heart among patients with HER2-positive BCA treated with contemporary RT.

Methods: A total of 47 women with HER2-positive BCA who were treated with an anthracycline, trastuzumab, and RT to the breast and/or chest wall +/- regional lymph nodes were included in this study. Two-dimensional echocardiography with speckle tracking imaging was performed at baseline (pre-chemotherapy), prior to and after RT (pre-RT and post-RT), and 6

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months post-RT. High sensitivity troponin I (hsTnI) was measured pre-RT and post-RT. Associations between mean heart dose (MHD) and changes in LV function after RT were examined in multivariable linear regression models.

Results: The MHD was 1.8 ± 1.5 Gy for patients receiving left-sided RT ($N = 26$) and 1.1 ± 1.3 Gy for patients receiving right-sided RT ($N = 21$). Pre-RT, post-RT, and 6-month post-RT echocardiograms were performed at median (interquartile range, IQR) of 49 days (27, 77) before and 54 days (25, 78) and 195 days (175, 226) after RT, respectively. Compared to pre-RT, a minimal decrease in LVEF was observed post-RT ($61 \pm 7\%$ vs. $59\% \pm 8\%$, $p = 0.003$) without any significant change in global longitudinal, circumferential, or radial strain, or diastolic indices at the post-RT timepoint. Median (IQR) concentrations of hsTnI decreased from 5.7 pg/ml (3.0, 8.7) pre-RT to 3.7 pg/ml (2.0, 5.9) post-RT. There was no significant change in systolic or diastolic indices of LV function at 6 months post-RT compared to pre-RT. MHD was not associated with changes in echocardiographic parameters of LV function after RT.

Conclusions: Breast RT using contemporary techniques can be delivered without evidence of early subclinical LV dysfunction or injury as measured by echocardiography and hsTnI in patients treated with anthracyclines and trastuzumab. Future studies should focus on identifying alternative biomarkers to elucidate early RT-induced cardiovascular effects and further characterizing long-term cardiovascular outcomes associated with contemporary breast RT.

Keywords

radiation; cardiotoxicity; breast cancer; strain

INTRODUCTION

Radiation therapy (RT) significantly improves survival for both early stage breast cancer patients following lumpectomy and for locally advanced patients following mastectomy.(1) However, breast RT has been associated with an increase in risk for cardiovascular morbidity and mortality due to the incidental radiation of cardiac structures.(2) A meta-analysis published in 2005 demonstrated a significantly increased risk of coronary heart disease (relative risk [RR] 1.30) and cardiac death (RR 1.38) in patients treated with RT versus without RT, with the caveat that the majority of included trials utilized outdated RT techniques.(3) A recent population-based case-control study by Darby et al. further demonstrated a linear increase in the risk of a major coronary event (i.e. myocardial infarction, coronary revascularization, or death from ischemic heart disease) with increasing doses of radiation to the heart.(4) Acute left ventricular (LV) systolic dysfunction after RT as assessed by left ventricular ejection fraction (LVEF) is an uncommon finding, with several studies showing no significant change up to 14 months after breast RT.(5–7) However, LV systolic dysfunction has been described as a late-effect of RT, particularly among cancer survivors who have received high doses of mediastinal RT.(8,9) Collectively, these studies provide a rationale to minimize the incidental radiation dose delivered to the heart from breast RT.

Contemporary radiation techniques now employ several strategies for cardiac sparing, including CT-based simulation, prone imaging,(10) and deep inspiratory breath holding.(11)

Highly conformal techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and proton therapy also reduce radiation dose to the heart and lungs. A major challenge to evaluating the benefit of these new techniques is the long latency period that exists between RT and subsequent cardiovascular events. Myocardial deformation imaging by speckle tracking echocardiography has been proposed as a non-invasive means of detecting early subclinical signs of RT-induced LV dysfunction. (12) The potential utility of circulating biomarkers, such as cardiac troponins, for identifying signs of early RT-induced myocardial injury has also been under active investigation.(13–15) If validated, these imaging and blood-based biomarkers could be useful to longitudinally characterize the adverse cardiovascular effects of RT or evaluate for differences in cardiovascular injury associated with standard versus newer RT techniques (e.g. proton therapy).

The risk of RT-induced cardiotoxicity is important in patients with HER2-positive breast cancer given their exposure to multiple cardiotoxic therapies such as anthracycline-based chemotherapy and trastuzumab +/- pertuzumab. In this study, the primary objective was to evaluate whether RT resulted in early changes to left ventricular function based on 2D echocardiographic assessment of left ventricular ejection fraction (LVEF), myocardial deformation indices including global longitudinal (GLS), radial (GRS), and circumferential strain (GCS), left ventricular diastolic indices, or high-sensitivity troponin I (hsTnI) in women with HER2-positive breast cancer treated with an anthracycline, trastuzumab, and post-operative RT. Secondly, we sought to determine whether changes in these echocardiographic parameters were associated with mean heart dose (MHD).

METHODS

Study design and population

We performed a retrospective RT substudy of patients who were enrolled in a cardiotoxicity monitoring and prevention study at our institution between July 2014 and April 2016. Briefly, 80 patients with HER2-positive early breast cancer (defined by immunohistochemistry (IHC 3+) or by a fluorescent in-situ hybridization HER2:CEP17 ratio of ≥ 2.0) and scheduled to undergo treatment with dose dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab +/- pertuzumab were enrolled and underwent 2D echocardiograms with speckle tracking at baseline (before chemotherapy), at the completion of doxorubicin and cyclophosphamide, and every 3 months during anti-HER2 therapy (~12 months duration) until the end of treatment. In addition, blood samples were obtained at baseline and every 3 months during anti-HER2 therapy until 6 months of treatment, processed, and stored at -80°C until the time of assay. For the present analysis, 48 patients underwent RT and were eligible for this study. One patient with incomplete radiation dose-volume data was excluded. RT was typically initiated about four weeks after completion of paclitaxel and administered concurrently with trastuzumab +/- pertuzumab. Written informed consent was obtained from all participants, and the study was approved by the Internal Review Board at Memorial Sloan Kettering Cancer Center.

Radiation therapy

Whole breast RT was delivered with tangential, 3D-conformal methods, or using IMRT. Regional nodal irradiation (RNI), when performed, included the supraclavicular, level I-III axillary, and internal mammary nodes (IMN). Prescription dose was 50 Gy in 25 fractions for RNI cases or 42.4 Gy in 16 fractions for breast-only cases. A 10 Gy boost was delivered to the lumpectomy cavity in women who received breast conserving therapy. For patients with left-sided tumors receiving RT in the supine position, treatment planning included both free-breathing (FB) and deep inspiratory breath hold scans. Multibeam IMRT treatment planning followed a previously reported technique.(16,17) The chest wall and lymph nodes were contoured as per published guidelines.(18) For all patients, the heart was defined from the pulmonary artery split superiorly to the left ventricle inferiorly following as previously described.(19) All MHDs were converted into equivalent doses in 2Gy fractions assuming $\alpha/\beta=3$ Gy,(20) and component RT plans were summed after fractionation correction.

Echocardiography

Conventional 2D and Doppler echocardiography were performed using a Vivid E9 ultrasound scanner (GE Medical Systems, Horten, Norway). Echocardiograms corresponding to the following timepoints were included for analysis: before chemotherapy (baseline), before initiation of RT (pre-RT), after completion of RT (post-RT), and at end of treatment (6-month post-RT). LVEF was calculated from the apical 4- and 2-chamber views using a modified Simpson biplane method according to the American Society of Echocardiography guidelines.(21) During the standard 2D echocardiogram, apical 2-, 3-, and 4- chamber views and short-axis views at the midpapillary level were acquired at a frame rate of 40-80 frames per second. Speckle tracking strain analysis was performed offline to calculate peak systolic GLS, GRS, and GCS (Echopac, GE Medical, Milwaukee, WI) as previously described.(22) All strain analysis was performed by one reader (A.Y.), independent of the clinical interpretation of the 2D echocardiogram. Inter- and intra-observer variability for GLS, GRS, and GCS were reported as mean error $\pm$ standard deviation in absolute values for 20 randomly selected studies. The intra-observer variability for GLS was $-0.01 \pm 0.64\%$, for GRS was $-1.86 \pm 11.96\%$, and for GCS was $1.29 \pm 2.17\%$. The inter-observer variability for GLS was $-0.61 \pm 0.88\%$, for GRS was $-0.07 \pm 12.87\%$, and for GCS was $-0.59 \pm 2.56\%$.

Biomarker assessment

Concentrations of hsTnI were measured using a fluorescent 1-step sandwich immunoassay (SMC TnI, Singulex, Inc., Alameda, California) with a lower limit of detection of 0.1 pg/ml. The 99th percentile reference limit of hsTnI among healthy females < 50 years and 50 years using this assay is 4.1 pg/ml and 5.9 pg/ml, respectively.(23) Blood samples corresponding to the baseline, pre-RT, and post-RT timepoints were included for analysis. For the post-RT timepoint, blood samples collected after completion of RT or up to 14 days prior completion of RT were included for analysis.

Statistical analysis

Descriptive statistics were used for patient characteristics. Continuous measures were summarized as mean and standard deviation or median and interquartile range (IQR) as appropriate, whereas categorical measures were summarized as frequency and percent. Comparisons of echocardiographic parameters before and after RT were made based on a Wilcoxon signed-rank test. A significant LVEF decline was defined as an absolute decrease of ≥ 10 percentage points to below the lower limit of normal ($< 53\%$) or an absolute decrease of ≥ 16 percentage points. Linear regression analysis was applied to study the change in LVEF and GLS after RT quantified as the % change in these echocardiographic measures from pre-RT to 6 months post-RT $[(6 \text{ months post-RT}) - (\text{pre-RT})/(\text{pre-RT})]$. Five covariates were investigated for their potential influence on RT-induced echocardiographic changes: age (continuous), hypertension (HTN; binary), MHD (continuous), baseline systolic blood pressure (SBP; continuous), and treatment with cardiac medications (i.e. beta-blocker, angiotensin converting enzyme inhibitor, or angiotensin receptor blocker; binary). Given multiple testing of hypotheses including five covariates per echocardiographic measure, a covariate was considered a predictor for the change in echocardiographic measures if the p-value from the associated linear regression was ≤ 0.01 (significant tendency: $p \leq 0.03$). Since the investigated cohort consisted of at most 47 patients, re-sampling was applied, and each linear regression was conducted over 1000 bootstrap samples. Measures of association (p-values and coefficient of determination; R^2) were reported as the median value across the 1000 bootstrap samples. All statistical analysis was performed in GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA) and MATLAB (v: R2016a, The MathWorks Inc., Natick, MA, US).

RESULTS

Study Population

Overall, 47 patients were evaluated and their demographics, cancer treatment, and cardiovascular risk factors are summarized in Table 1. Patients were treated with dose dense doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks for four cycles with pegfilgrastim, followed by weekly paclitaxel (80 mg/m^2) for 12 weeks and trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) every 3 weeks from the start of paclitaxel. Forty-three patients (91%) received dual anti-HER2 therapy with pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks). At baseline prior to beginning chemotherapy, all patients had a normal LVEF (median 65%, range 53-75%, Table 2).

Of the 47 patients studied, 26 (55%) had left-sided and 21 (45%) had right-sided breast cancer. RT was initiated a median (IQR) of 151 days (124, 162.5) after starting trastuzumab. 3D conformal radiation therapy was delivered in 37 patients and IMRT in 10 patients. Sixteen (34%) patients received RNI. The mean heart dose (MHD) was $1.5 \pm 1.5 \text{ Gy}$ and the max heart dose was $28.3 \pm 19.0 \text{ Gy}$. Eleven patients received a MHD $> 2 \text{ Gy}$ (mean $4.0 \pm 1.0 \text{ Gy}$). The MHD was $1.8 \pm 1.5 \text{ Gy}$ for patients receiving left-sided RT ($N = 26$) and $1.1 \pm 1.3 \text{ Gy}$ for patients receiving right-sided RT ($N = 21$). Patients undergoing RNI had a higher MHD compared to patients undergoing whole breast RT alone ($2.4 \pm 1.9 \text{ Gy}$ vs. 1.1 ± 1.1 , $p=0.006$).

Effect of radiation therapy on LVEF and diastolic function

The pre-RT, post-RT, and 6-month post-RT echocardiograms were performed a median (IQR) of 49 days (27, 77) before, and 54 (25, 78) and 195 (175, 226) days after RT, respectively. A decline in mean LVEF was observed from baseline to the pre-RT echocardiogram ($65 \pm 4\%$ vs. $61 \pm 7\%$, $p < 0.001$), with 3 out of 47 patients developing a significant decline in LVEF of $> 10\%$ to below the lower limit of normal, which reflect changes corresponding to the anthracycline and early taxane and anti-HER2 treatment period. When compared to pre-RT, the post-RT echocardiogram showed a decrease in LVEF ($61 \pm 7\%$ vs. $59 \pm 8\%$, $p=0.004$) but not in diastolic indices. At 6 months post-RT, there was no significant difference in LVEF or diastolic indices compared to pre-RT (Table 2).

Effect of radiation therapy on myocardial strain and hsTnI

Longitudinal strain analysis was not feasible in 3 patients at baseline, 1 at the post-RT timepoint, and 3 at the 6-month post-RT timepoint. Circumferential and radial strain analysis was not feasible in 6 patients at baseline, 4 patients pre-RT, 3 patients post-RT, and 9 at the 6-month post-RT timepoint. A decline in GLS was observed from baseline to pre-RT ($-20.7 \pm 2.0\%$ vs. $-18.9 \pm 2.8\%$, $p < 0.001$), corresponding to the anthracycline and early taxane and anti-HER2 treatment period. Overall, compared to pre-RT, there was no significant difference in GLS, GCS, or GRS at the post-RT or 6-month post-RT echocardiograms (Figure 1). Eight patients developed a relative decline in GLS (defined as a greater than 15% absolute change) at 6 months post-RT, of which 1 was noted to have a significant LVEF decline (55% at pre-RT, 41% at post-RT, and 45% at 6-month post-RT) and none had signs or symptoms of clinical heart failure.

In total, paired pre-RT and post-RT blood samples were available for hsTnI testing in 28 of 47 patients and were included for analysis. Paired samples were unavailable in 19 patients due to the following: withdrawal of consent for research blood collection ($n=3$), protocol deviation ($n=3$), and absence of a blood sample in the post-RT timepoint ($n=13$). The pre-RT and post-RT blood samples were collected a median (IQR) of 52 days (22, 70) before and 22 days (1, 44) after RT, respectively. Median (IQR) concentrations of hsTnI increased from 0.4 pg/ml (0.2, 0.7) at baseline to 5.7 pg/ml (3.0, 8.7) at the pre-RT timepoint, corresponding to the anthracycline and early trastuzumab treatment period, then subsequently decreased to 3.7 pg/ml (2.0, 5.9) at the post-RT timepoint.

Association between radiation dose parameters and changes in LV function

MHD was not predictive of changes in LVEF or GLS during RT (Table 3). Similarly, other covariates including age, hypertension, baseline systolic blood pressure, and cardiac medications were not predictive of changes in LVEF or GLS. The MHD covariate for GLS presented with the lowest p-value ($p=0.17$; $R^2=0.02$), and in a subsequent analysis, four alternative heart dose parameterizations were investigated: the maximum dose (D_{max}), the minimum dose (D_{min}), as well as the relative cardiac volume receiving at least 5Gy and 30Gy (V_5 and V_{30}). Both the D_{min} and V_5 presented with corresponding tendencies ($p=0.14$, 0.12 ; $R^2=0.03$, 0.03), but similar to MHD, statistically significant relationships were not established. RT-induced changes in GCS and GRS were not investigated further due to complete data being available for only 34 of 47 patients.

DISCUSSION

In this single-center study of women with HER2-positive breast cancer treated with anthracycline chemotherapy followed by trastuzumab-based therapy and adjuvant RT, we employed 2D echocardiography with speckle tracking imaging and hsTnI to evaluate for early subclinical RT-induced changes in LV systolic and diastolic function. We found no significant change in myocardial strain indices (GLS, GCS, or GRS) at a median of 2 and 6 months after RT, nor any increase in hsTnI after RT. Furthermore, we did not observe any association between MHD or other radiation dose parameters and changes in LVEF or GLS. Findings from this study suggest that RT using contemporary techniques can be delivered without evidence of early subclinical LV dysfunction as measured by echocardiography in patients treated with other sequential cardiotoxic therapies including anthracycline chemotherapy and trastuzumab +/- pertuzumab.

Considerable efforts have focused on improving radiation delivery and developing safer methods to minimize radiation exposure to adjacent organs at risk, such as the heart, without compromising target coverage or treatment efficacy. Proton therapy is one such approach that in many cases can minimize the radiation dose to the heart beyond what has been achievable with photon-based cardiac avoidance techniques (i.e. cardiac shielding, deep inspiratory breath hold, or prone positioning). However, a careful assessment of the effectiveness of new, resource-intensive technologies is needed prior to their routine adoption. A major challenge in assessing the potential cardiovascular benefit of new radiation techniques is the long latency period between the time of initial radiation exposure and subsequent cardiac events, which can occur years or decades after the initial radiation exposure. The RADCOMP trial (NCT02603341) is a randomized trial comparing protons versus photons with a primary endpoint of 10-year major cardiac events (MCE). This trial needs to accrue 1,700 patients in 5 years to show a 40% reduction in 10-year rates of MCE. There are no intermediate biomarkers/surrogates built into this study since there are still no widely accepted imaging modalities to detect RT-related subclinical cardiac injury. And while this study has already accrued more than 400 patients, we will need to wait at least another 15 years for the final results of this study. Interestingly, none of the current techniques used such as heart blocks, IMRT, prone, or deep inspiratory breath hold, have even been shown to reduce cardiotoxicity. They have been adopted based on their ability to limit radiation exposure to the heart, and the hope that this will reduce cardiotoxicity. This has led to growing interest in identifying surrogate endpoints, either imaging or blood-based, for late cardiac outcomes that could help assess the utility of novel radiation techniques.

In contrast to our findings, limited reports have demonstrated early subclinical changes in LV function after RT using non-invasive cardiovascular imaging modalities. In a study of 114 patients with left-sided breast cancer, nuclear cardiac perfusion imaging with single photon emission computed tomography (SPECT) demonstrated new perfusion defects with corresponding wall-motion abnormalities after RT.(24) Other studies have reported on the use of speckle tracking strain echocardiography to detect subclinical RT-induced cardiotoxicity. Among breast cancer patients treated with adjuvant RT, a decrease in GLS was observed both early (immediately after and at 2 months) and late (8 and 14 months) after left-sided RT with a MHD ranging from 7-9 Gy.(5,6) More recently, Lo et al. reported

decrements in global and segmental myocardial deformation among chemotherapy naïve breast cancer patients undergoing adjuvant RT alone with a MHD of 2.5 Gy.(7,25). There are a few possible explanations for the absence of RT-induced changes in GLS in the current study. First, to our knowledge this is the first study to evaluate for subclinical RT-induced cardiotoxicity in HER2-positive patients treated with both anthracyclines and trastuzumab +/- pertuzumab. We did observe a decline in both LVEF (65% to 61%) and GLS (21% to 19%) from baseline to pre-RT, reflecting changes in LV systolic function related to anthracycline chemotherapy and trastuzumab +/- pertuzumab, which have been well described.(26) However, if breast RT putatively contributes to further myocardial injury, it is possible that the magnitude of RT-induced injury with contemporary RT techniques is below the threshold detectable using myocardial deformation imaging. Second, the MHD in our study of 1.5 Gy was lower compared to prior studies evaluating RT-associated cardiotoxicity, (5–7,25) although this low MHD is reflective of contemporary RT techniques that are standard of care at our institution

It is important to note that while there were no significant changes in GLS after RT, a minimal decline in LVEF was noted at post-RT compared to pre-RT. This highlights one of the commonly cited limitations of 2D echocardiography for the assessment of longitudinal changes in LV systolic function during cancer therapy, specifically the high temporal variability of 2D LVEF measurements. In a study by Thavendiranathan et al. on the reproducibility of various LVEF assessment techniques, the temporal variability of 2D LVEF was approximately 10% among breast cancer patients without cardiotoxicity who had stable GLS.(27) In our study, the minimal decline in LVEF after RT with no significant change in GLS likely reflects this temporal variability inherent to 2D LVEF measurement technique rather than a true change in LV systolic function due to a cardiotoxic effect. We also demonstrated that there was no interval increase in hsTnI immediately following RT, further supporting the absence of any significant acute myocardial injury associated with contemporary breast RT. Our findings are consistent with prior studies that have failed to show a significant increase in troponin levels among patients with breast or lung cancer treated with chest radiation.(15,28,29)

Findings from this study raise several important questions. First, in the absence of changes in deformation indices with contemporary RT, investigation into other biomarkers of vascular or endothelial injury (i.e. fractional flow reserve or flow mediated dilatation) may be warranted given that endothelial dysfunction and subsequent microvascular and/or macrovascular ischemia are proposed mechanisms of RT-induced injury.(30) Second, when declines in GLS are observed after higher doses of radiation, it remains unclear whether this surrogate marker is associated with risk for late cardiac events. Finally, a careful assessment of the cost-effectiveness of more expensive RT techniques that are capable of reducing radiation dose to the heart is needed. One prior cost-effectiveness study based on Markov modeling failed to show that proton therapy was cost-effective in women with breast cancer receiving a MHD < 5 Gy.(31) Additional studies in HER2-positive breast cancer patients who are at increased risk for cardiotoxicity may help provide insight into determining whether further reductions of radiation dose to the heart are indicated.

This study has several limitations, the first of which is the small sample size. However, to our knowledge this is the first study to investigate the role of myocardial strain imaging to detect subclinical RT-induced cardiotoxicity in patients with HER2-positive breast cancer treated with anthracyclines and trastuzumab +/- pertuzumab. Second, although no significant change in overall GLS was observed after approximately 6 months of follow-up, 8 of 47 (17%) patients were noted to have a significant decline in GLS. It is possible that further differences in GLS could be identified with additional follow-up beyond 6 months, warranting further investigation. Third, we cannot rule out the possibility that patients treated with other non-anthracycline or non-trastuzumab based treatment regimens may develop early changes in LV function with contemporary RT. However, the multiple-hit hypothesis would suggest that exposure of breast cancer patients to multiple sequential or concurrent cardiovascular insults (i.e. anthracycline chemotherapy, anti-HER2 therapy, and/or RT) may enhance susceptibility to further cardiovascular injury.(32) We included patients receiving a regimen associated with high cardiotoxicity risk (i.e. anthracyclines followed by anti-HER2 therapy and breast RT) to provide the highest likelihood for detecting subclinical RT-induced changes in LV function. While the overall MHD in this study was low, this reflects ongoing efforts to optimize cardiac sparing in current standard-of-care practice. Finally, formal comparison testing of hsTnI concentrations could not be performed due to incomplete paired samples in 19 patients. The strengths of this study include comprehensive prospective collection of echocardiographic data, uniform treatment exposure of all patients to anthracyclines followed by trastuzumab +/- pertuzumab, and myocardial strain analysis performed by a single experienced echocardiographer.

CONCLUSIONS

In HER2-positive breast cancer patients receiving cardiotoxic cancer therapy, contemporary breast RT can be delivered without evidence of early subclinical LV dysfunction or injury as measured by 2D echocardiography with myocardial strain imaging and hsTnI. Future studies should focus on identifying alternative biomarkers to elucidate early RT-induced cardiovascular effects and further characterizing long-term cardiovascular outcomes associated with contemporary breast RT.

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Figure 1.

Time course of left ventricular ejection fraction (**A**), global longitudinal strain (**B**), global circumferential strain (**C**), and global radial strain (**D**) after breast radiation therapy. For LVEF, $p < 0.05$ for post-RT (*) compared to pre-RT. For GLS, GCS, and GRS, $p > 0.05$ for all post-RT and 6-month post-RT timepoints compared with pre-RT.

Pre-RT, pre-radiation therapy; Post-RT, post-radiation therapy

Table 1.

Baseline characteristics

Age at diagnosis (y), median (range)	52 (29-68)
Body mass index, median (range)	27.1 (18.3-36.5)
<= 25	15 (32)
25-29	19 (40)
>= 30	13 (28)
Histologic type:	
Ductal	47 (100)
Hormone receptor status	
Positive	24 (51)
Negative	23 (49)
Cancer stage	
Operable (T1-2, N0-1, M0)	
<i>Stage I</i>	5 (11)
<i>Stage II/III</i>	33 (70)
Locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M)	9 (19)
Surgery type:	
Mastectomy	16 (34)
Breast conserving	31 (66)
Cumulative doxorubicin dose (mg/m ²), median (range)	240 (120-240)
Cumulative trastuzumab dose (mg/kg), median (range)	110 (32-140)
RT Treatment	
Left	26 (55)
Right	21 (45)
Mean Heart Dose (Gy), mean $\pm$ SD	1.5 $\pm$ 1.5
IMRT	10 (21)
Nodal RT	16 (34)
Cardiovascular risk factors	
Hypertension	8 (17)
Diabetes mellitus	4 (9)
Hyperlipidemia	5 (11)
Coronary artery disease	0 (0)
Smoking	14 (30)
Cardiovascular treatment	
Beta-blockers	3 (6)
ACE-inhibitor/ARB	6 (13)

Race/Ethnicity	
Non-hispanic white	25 (53)
Non-hispanic black	8 (17)
Hispanic	7 (15)
Asian	7 (15)

Data given as no. (%) unless otherwise indicated

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; Gy, gray; IMRT, intensity-modulated radiotherapy; RT, radiotherapy

Table 2.

Summary of echocardiographic parameters during breast radiotherapy

	Baseline	Pre-RT	Post-RT	6-month post-RT
LVEF (%)				
Median	65	62	61	61
Range	53 – 75	35 – 76	33 – 66	35 – 74
Mean $\pm$ SD	65.3 $\pm$ 4.1	60.9 $\pm$ 7.3 *	58.7 $\pm$ 7.6 †	60.4 $\pm$ 6.9
Longitudinal Strain (%)				
A3C	-20.4 $\pm$ 2.5	-18.6 $\pm$ 2.7	-18.4 $\pm$ 3.2	-18.5 $\pm$ 2.9
A4C	-20.5 $\pm$ 2.1	-18.7 $\pm$ 2.8	-18.6 $\pm$ 2.8	-18.3 $\pm$ 2.2
A2C	-21.4 $\pm$ 2.8	-19.3 $\pm$ 3.5	-19.1 $\pm$ 3.3	-19.1 $\pm$ 2.5
Global	-20.7 $\pm$ 2.0	-18.9 $\pm$ 2.8 *	-18.7 $\pm$ 3.0	-18.6 $\pm$ 2.3
Circumferential strain (%)	-18.9 $\pm$ 4.0	-16.5 $\pm$ 3.7	-17.4 $\pm$ 3.3	-16.2 $\pm$ 4.3
Radial Strain (%)	42.5 $\pm$ 16.5	40.2 $\pm$ 17.6	41.7 $\pm$ 24.8	36.3 $\pm$ 15.0
Diastolic Parameters				
Mitral E velocity (cm/sec)	79.8 $\pm$ 18.2	82.5 $\pm$ 15.2	78.9 $\pm$ 12.9	77.8 $\pm$ 16.5
Mitral A velocity (cm/sec)	75.3 $\pm$ 16.0	74.8 $\pm$ 19.9	70.6 $\pm$ 16.4	72.5 $\pm$ 17.6
Mitral E/A ratio	1.1 $\pm$ 0.4	1.2 $\pm$ 0.4	1.2 $\pm$ 0.4	1.1 $\pm$ 0.4
Septal e' (cm/sec)	9.0 $\pm$ 2.45	9.2 $\pm$ 2.3	8.9 $\pm$ 2.3	8.8 $\pm$ 2.5
Lateral e' (cm/sec)	12.0 $\pm$ 3.5	11.5 $\pm$ 3.8	11.2 $\pm$ 3.4	11.3 $\pm$ 3.4
Septal E/e' ratio	9.2 $\pm$ 2.4	9.4 $\pm$ 2.2	9.2 $\pm$ 2.1	9.4 $\pm$ 3.0
Lateral E/e' ratio	7.0 $\pm$ 1.8	7.9 $\pm$ 2.4	7.5 $\pm$ 2.1	7.3 $\pm$ 2.3

Data given median (range), unless otherwise specified

* $p < 0.05$ for comparison with baseline echocardiogram† $p < 0.05$ for comparison with pre-RT echocardiogram

LA, left atrial; LV, left ventricular, LVEDd, left ventricular end diastolic diameter; BSA, body surface area, LVEF, left ventricular ejection fraction; A3C, apical 3 chamber; A4C, apical 4 chamber; A2C, apical 2 chamber

Table 3.

Univariate linear regression analysis of changes in LVEF and GLS.

Endpoint	N	Covariate	R ²	p - value
% change LVEF ^a	47	Age	-0.007	0.413
		HTN	-0.009	0.443
		MHD	-0.007	0.411
		SBP	-0.013	0.524
		Cardiac Meds	-0.012	0.514
% change GLS ^b	43	Age	-0.016	0.571
		HTN	-0.010	0.457
		MHD	0.021	0.174
		SBP	-0.004	0.372
		Cardiac Meds	-0.015	0.540

^a % change LVEF = $(\text{LVEF}_{6\text{monthpostRT}} - \text{LVEF}_{\text{pre-RT}}) / \text{LVEF}_{\text{pre-RT}}$

^b % change GLS = $(\text{GLS}_{6\text{monthpostRT}} - \text{GLS}_{\text{pre-RT}}) / \text{GLS}_{\text{pre-RT}}$

LVEF, left ventricular ejection fraction; GLS, global longitudinal strain

Note: R² and p-values are given as the median value over the 1000 Bootstrap samples.