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Original Article

Persistent reduction in global longitudinal strain in the longer term after radiation therapy in patients with breast cancer

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ABSTRACT

Background: More than 80% of breast cancer patients receive radiotherapy (RT). However, RT can lead to cardiotoxicity, which usually develops insidiously over years, making diagnosis difficult. It is also unknown whether early identification of at-risk patients might improve long-term outcome. We have previously described subclinical alterations, detected by two-dimensional speckle tracking strain echocardiography, in left ventricular (LV) function immediately following RT in breast cancer.
Hypothesis: Subclinical myocardial alterations in LV function consequent to RT cardiotoxicity, observed early, persist at 12 months.
Methods: 40 chemotherapy naive women with left-sided breast cancer, treated with surgery and adjuvant breast RT, were prospectively recruited from two tertiary hospitals. Transthoracic echocardiography was performed at baseline (pre-RT), 6 weeks post-RT, and 12 months post-RT.
Results: An increase in LV end diastolic and end systolic volumes was seen from baseline, consistent with persistent LV remodelling; however, due to the increase in both systolic and diastolic volumes over time, no change in LV ejection fraction (EF) was observed. Global longitudinal strain (GLS) and S′ velocity remained significantly lower at 12 months post-RT. GLS dropped by >10% in 16 patients and by >20% in 4 patients compared to baseline.
Conclusions: Subclinical cardiac dysfunction using strain analysis, evident early, persists one year after RT, despite unchanged conventional indices such as LVEF. Persistent GLS reduction may be of particular importance in breast cancer patients receiving concomitant chemotherapy. Longer term prospective studies are required to determine if reductions in strain post-RT are associated with future adverse cardiovascular events.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women globally, accounting for 23% (~1.38 million) of the total of new cancer cases [1]. More than 80% of breast cancer patients receive radiation therapy (RT) as part of disease management [2]. RT reduces breast cancer recurrence and improves survival [3,4]. However, RT can lead to cardiotoxicity, with adverse events often observed in a dose-dependent manner [5–7]. Radiation-induced cardiac injury usually develops over a prolonged period of time, making diagnosis more difficult, and initial compensatory cardiac response can further delay the recognition of injury for many years [5].

Two dimensional (2D) speckle tracking strain echocardiography (STE) is a new semi-automated echocardiographic technique that tracks movement of myocardial speckles within tissues, frame-by-frame, over the cardiac cycle thereby cataloguing their spatiotemporal displacement and providing unique information about global and segmental myocardial deformation [8]. Strain describes myocardial deformation as the relative change in length, whilst strain rate refers to the rate at which this change in length occurs [9]. The utility of 2D strain echocardiography in the identification

Abbreviations: RT, radiotherapy; LV, left ventricular; EF, ejection fraction; GLS, global longitudinal strain; 2D, two dimensional; STE, speckle tracking strain echocardiography; CT, computed tomography; TTE, transthoracic echocardiogram; S-Sr, global systolic strain rate; E-Sr, early diastolic strain rate; A-Sr, late diastolic strain rate; E, early diastolic filling velocity; A, late diastolic filling velocity; DT, deceleration time; TDI, tissue Doppler imaging; LA, left atrium; BSA, body surface area; ANOVA, repeated-measures analysis of variance; MHD, mean heart dose; EDV, end diastolic volume; ESV, end systolic volume.

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of subclinical myocardial changes in a variety of conditions, including hypertension, diabetes mellitus, infiltrative cardiomyopathies, and chemotherapy-related cardiotoxicity, has been demonstrated [10–13]. Our group has previously described subclinical alterations detected by strain imaging in left ventricular (LV) systolic [14] and diastolic function [15] immediately following RT. However, there are sparse data regarding longer term cardiac effects of RT and the utility of strain imaging to investigate these myocardial changes if present.

Our aim was to determine whether the early changes observed in LV strain measurements following RT would persist at 12-month follow-up. We have previously reported LV systolic and diastolic function alterations using traditional echocardiographic parameters as well as 2D strain analysis at 6 weeks post-RT in this cohort of 40 chemotherapy naïve women with left-sided breast cancer. We hypothesised that subclinical myocardial changes in LV systolic and diastolic function consequent to cardiotoxic effects of RT, observed early after RT would persist at 12 months.

Methods and materials

Patient population

Fifty-eight consecutive female patients with left-sided breast cancer were prospectively screened of whom 40 patients were recruited from two western Sydney tertiary hospitals (Campbelltown and Liverpool Hospitals, Sydney, Australia) from April 2009 to November 2012. Inclusion criteria were chemotherapy naïve patients with histologically confirmed left-sided breast cancer, treated with breast conservation surgery (lumpectomy) and adjuvant breast RT with no nodal RT. Recruitment took longer than anticipated as the inclusion criteria were very specific. Hormonal treatment was administered in patients who were hormone receptor positive. Exclusion criteria were prior chemotherapy or RT, previous ischaemic heart disease, heart failure, or significant valvular heart disease (defined as more than mild valvular regurgitation or stenosis). Written informed consent was obtained from all recruited patients. The study protocol was approved by the hospital and local area health service ethics committee (SSWAHS HREC no. ECOO136).

Radiation technique

During RT planning, a non-contrast, planning computed tomography (CT) scan was performed on all patients pre-treatment. Breast RT was performed with tangential photon beams; attempts were made to minimise the volume of the heart in the RT field, although no attempts were made to shield the heart if this compromised the dose administered to the breast. Patients were treated supine on a breast board with 6 MV and/or a mix of 6 MV and 18 MV. Treatment was either standard (50 Gy in 25 fractions) or hypofractionated (42.4 Gy in 16 fractions). An additional dose of 10 Gy–16 Gy in 2 Gy fractions was delivered using electrons for some patients.

Radiation dose–function relationship

The RT planning CT images were imported into a 3-dimensional treatment planning system (Xio V4.4.0; Elekta, Stockholm, Sweden). As detailed previously, these images were positioned to match the echocardiographic apical 4-chamber view, with myocardial segments identified correspondingly with the segmental LV analysis typically performed on echocardiography [14]. The extent of specific areas of heart tissue exposed to RT was ascertained. Dose–volume histograms were analysed for mean heart dose, mean LV dose and the volume of heart receiving 25 Gy (V25) and 30 Gy (V30) as previously reported [14].

Echocardiographic examination

A comprehensive transthoracic echocardiogram (TTE) was performed at baseline (pre-RT), 6 weeks post-RT, and 12 months post-RT. All TTEs were performed using Vivid 7 or E9 ultrasound scanners (GE Vingmed, Horten, Norway) equipped with a 2.5-MHz broadband transducer. Patients were placed in the left lateral decubitus position and frame-rate optimised ($\geq$60 frames per second) images from standard views including the apical 2-,3-, and 4-chamber views and mid-level short axis views were obtained for offline analysis. 2D, Doppler, and M-mode measurements were also performed. An average of three measurements was used for the final analysis.

Echocardiographic measurements

LV systolic function was evaluated by LV ejection fraction (EF), using the Simpson's biplane method of discs [16]. 2D STE strain analysis was performed using dedicated software (Echopac, GE Vingmed) to measure LV global longitudinal strain (GLS). Additionally, global systolic (S-Sr), early diastolic (E-Sr) and late diastolic (A-Sr) strain rates were measured.

The strain traces were obtained through semi-automated tissue tracking in the apical four, two, and three chamber views. An average of three cardiac cycles were analysed for each view [14].

With regard to LV diastolic function, mitral inflow analysis was obtained using pulsed wave Doppler from the apical 4-chamber view, with the sample volume placed at the tips of the mitral valve leaflets. The peak early (E) and late (A) diastolic filling velocities, E/A ratio and E-wave deceleration time (DT) were determined. Tissue Doppler Imaging (TDI) was used to determine the E′ and A′ velocity by placing the sample volume at the septal and lateral mitral annulus. An average E/E′ was then calculated using an average of the septal and lateral E′ velocities.

Maximum and minimum biplane left atrial (LA) volumes were measured at three distinct time points in the cardiac cycle from the apical 4- and 2-chamber zoomed views, using the biplane method of discs [17]. Maximal LA volume was measured immediately prior to mitral valve opening, and minimal LA volume was measured at mitral valve closure. These LA volumes were indexed to body surface area (BSA) in all patients [18].

Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as percentages. Categorical variables were compared using Fisher's chi squared tests. Repeated-measures analysis of variance (ANOVA) was performed to investigate differences in outcome variables within patients across three timepoints (pre-RT, 6 weeks post-RT, and 12 months post-RT). The Mauchly test of sphericity was used with the Greenhouse–Geisser correction. The Spearman technique was used to assess correlations between variables. Unpaired t-tests were used to compare means between two independent variables. Statistical analysis was performed using SPSS software (IBM Corporation, Version 25, Armonk, New York).

Results

Patient population

Fifty-eight female breast cancer patients were initially screened, with 18 subsequently excluded; 8 did not fulfil inclusion

criteria, 6 withdrew consent, and 4 patients had technically non-diagnostic echocardiograms. Forty patients were prospectively enroled and underwent serial echocardiograms at baseline, and 6 weeks post-RT. Thirty-seven patients agreed to undergo a 12-month TTE (no patient in this group received any chemotherapy). Strain measurements were not performed for one patient at baseline but all other baseline echocardiographic measurements were performed.

All patients were in sinus rhythm on baseline ECG, with no history of arrhythmias. Twenty-two patients with hormonal receptor sensitivity were administered hormonal treatment after their radiation. The baseline patient demographics and cardiovascular risk factors are presented in Table 1. With regard to prevalence of cardiovascular risk factors, 33% of patients had a history of smoking, 20% had diabetes, 43% had hypertension, 53% had dyslipidaemia, and 15% had a family history of ischaemic heart disease.

Radiation therapy protocol

Thirty patients received the standard RT fractionation and ten received the hypofractionated treatment. Average mean heart dose (MHD) and mean LV dose were 2.5 ± 1.3 Gy and 4.8 ± 2.7 Gy respectively. Mean V25 and V30 doses were 2.5 ± 2.1% and 2.2 ± 2.0% respectively. Booster RT doses were given to 30 patients.

Echocardiographic parameters

LV volumes and EF/pericardium

LV volumes and EF were normal at baseline and at 12-month follow-up. At follow-up (12 months), there was no significant change in LVEF. However, mean end-diastolic volume (EDV) and end-systolic volume (ESV) progressively increased compared to their baseline value (Table 2 and Fig. 1). Seven patients had a >10% reduction in EF compared to their baseline values at 12-month follow-up, with LVEF remaining within clinically normal range in all patients. Whilst acute pericardial changes can be observed following radiation, we did not observe any pericardial effusion or thickening in the study patients at any of the time points.

Diastolic parameters

Overall, more than half of all patients with diastolic dysfunction had hypertension (9/15, 60%).

Peak E velocity was unchanged, though peak A velocity increased significantly over 12 months. As a consequence, the mean E/A ratio was significantly lower at 12-month follow-up. No significant differences were noted in other diastolic parameters, including deceleration time, and average E′ velocity (Table 2). There was no significant change in the deceleration time over serial follow-up. The average E′ values at 12-month follow-up were similar to those measured at 6 weeks. The global E-Sr, a measure of diastolic dysfunction was significantly reduced at 12-month follow-up, whilst in contrast, the global A-Sr significantly increased at 12 months (Table 2).

Table 1
Patient demographics.

Parameter	Mean ± SD/frequency (%)	Range
Age (years)	60.2 ± 9.1	40–77
Height (cm)	160.3 ± 6.2	145.5–176
Weight (kg)	74.0 ± 15.9	48–114
Body mass index (kg/m^2)	28.8 ± 6.1	18.75 ± 45.67
Systolic blood pressure (mmHg)	132 ± 18	100–170
Diastolic blood pressure (mmHg)	77 ± 8	59–88
Mean dose to breast (Gy)	58.9 ± 9.5	42.4–66
Mean V30 heart (%)	2.2 ± 2.0	0–8.29
Mean V25 heart (%)	2.5 ± 2.1	0.01–8.94
Mean heart dose (Gy)	2.5 ± 1.3	0.88–8.94
Mean LV dose (Gy)	4.8 ± 2.7	1.18–12.15
Smoking (%)	13 (32.5)	–
Diabetes (%)	8 (20)	–
Hypertension (%)	17 (42.5)	–
Dyslipidaemia (%)	21 (52.5)	–
Family history of IHD (%)	6 (15)	–

Abbreviations: LV = left ventricular; IHD = ischaemic heart disease.

Systolic parameters

A reduction in the average S′ was noted over 12-month follow-up. These changes were more prominent at 12-month follow-up than during intermediate follow-up (6 weeks).

Strain parameters

A significant reduction in GLS was observed across the three time-points that were evaluated (i.e. at baseline prior to RT, at 6 weeks post-RT and at 12 months post-RT). Although the change in GLS was most pronounced within the first six weeks of RT, a significant reduction in GLS persisted at 12-month follow-up. A mean reduction of 7.9 ± 5% of the baseline value was noted with 12/37 (32%) of patients dropping their average GLS by >10% from baseline (Fig. 1).

There were 16 patients who continued to drop GLS at each timepoint compared to the previous value, and 17 patients in whom the GLS either remained unchanged or demonstrated a degree of improvement at either early (6 weeks) or 12-month follow-up. Patients with the persistent GLS drop (n = 16), had a significantly higher ESV and lower EF at 12-month follow-up compared to those that did not have a sustained, ongoing drop in GLS (ESV: 39 ± 12 vs. 30 ± 5 mL; p = 0.006; EF: 60 ± 4% vs. 64 ± 4%, p = 0.005). The EDV was also higher in this subgroup, with a trend to significance (EDV: 97 ± 25 vs. 83 ± 14 mL; p = 0.056) (Table 3).

Significant early reduction in the global S-Sr, E-Sr and A-Sr strain rates were also observed (Fig. 2) with subsequent improvement in strain rates over 12-month follow-up. S-Sr appeared to normalise, E-Sr improved but was still lower than baseline, whilst A-Sr increased at 12-month follow-up.

RT dose

A correlation between radiation dose and change in GLS at 6 weeks post-RT was previously reported [14]. We performed subgroup analysis between those with <10% and >10% reduction in LVEF and GLS. There were no significant differences in mean heart or mean LV radiation dose received by patients who had a >10% reduction in either EF or GLS compared to those with < 10% reduction or no reduction.

Hormonal therapy

A subgroup analysis of those patients who received hormone therapy (n = 13) versus those who did not, demonstrated no significant differences in echocardiographic parameters, including GLS between the two groups (data not shown).

Discussion

We have demonstrated three important findings with respect to 12-month cardiotoxicity following RT, in chemotherapy naïve left-sided breast cancer patients. Firstly, although there is no significant 12-month reduction in the conventionally measured LVEF, the GLS and S′ velocity remained significantly lower at 12-month follow-up. Secondly, cardiac remodelling was present with significant increases in EDV and ESV at 12-month follow-up. Thirdly, those with persistent and sustained reductions of >10% of GLS had a sig-

Table 2
LV size, systolic, diastolic function and strain.

	Mean ± SD (Baseline)	Mean ± SD (6 weeks post RT)	Mean ± SD (12 months)	*P* value (ANOVA RM)
Systolic function				
Biplane EDV (mL)	73.0 ± 22	79.9 ± 20	89.8 ± 21	<0.001
Biplane ESV (mL)	27.9 ± 10	30.3 ± 10	34.3 ± 10	<0.002
Ejection Fraction (%)	62.2 ± 5	62.5 ± 4	62.0 ± 4	0.785
Average S′ (cm/s)	7.0 ± 1	6.9 ± 1	6.4 ± 1	0.02
Diastolic parameters				
Peak E	0.65 ± 0.16	0.66 ± 0.16	0.66 ± 0.22	0.95
Peak A	0.69 ± 0.17	0.71 ± 0.20	0.77 ± 0.15	0.004
Average E′(cm/s)	8.0 ± 2	7.9 ± 2	8.3 ± 2.5	0.42
E/A ratio	1.03 ± 0.4	0.99 ± 0.3	0.85 ± 0.3	<0.01
Deceleration Time (ms)	210 ± 11	228 ± 8	251 ± 7	0.14
Strain				
Average GLS (%)	−20.6 ± 2	−18.9 ± 2	−18.9 ± 3	<0.001
Average global S Sr (s^{-1})	−1.15 ± 0.1	−1.04 ± 0.2	−1.21 ± 0.2	0.05
Global E Sr (s^{-1})	1.38 ± 0.2	1.23 ± 0.2	1.34 ± 0.3	<0.001
Global A Sr (s^{-1})	1.12 ± 0.2	1.03 ± 0.2	1.30 ± 0.2	<0.43

Abbreviations: EDV = end diastolic volume; ESV = end systolic volume; GLS = global longitudinal strain.

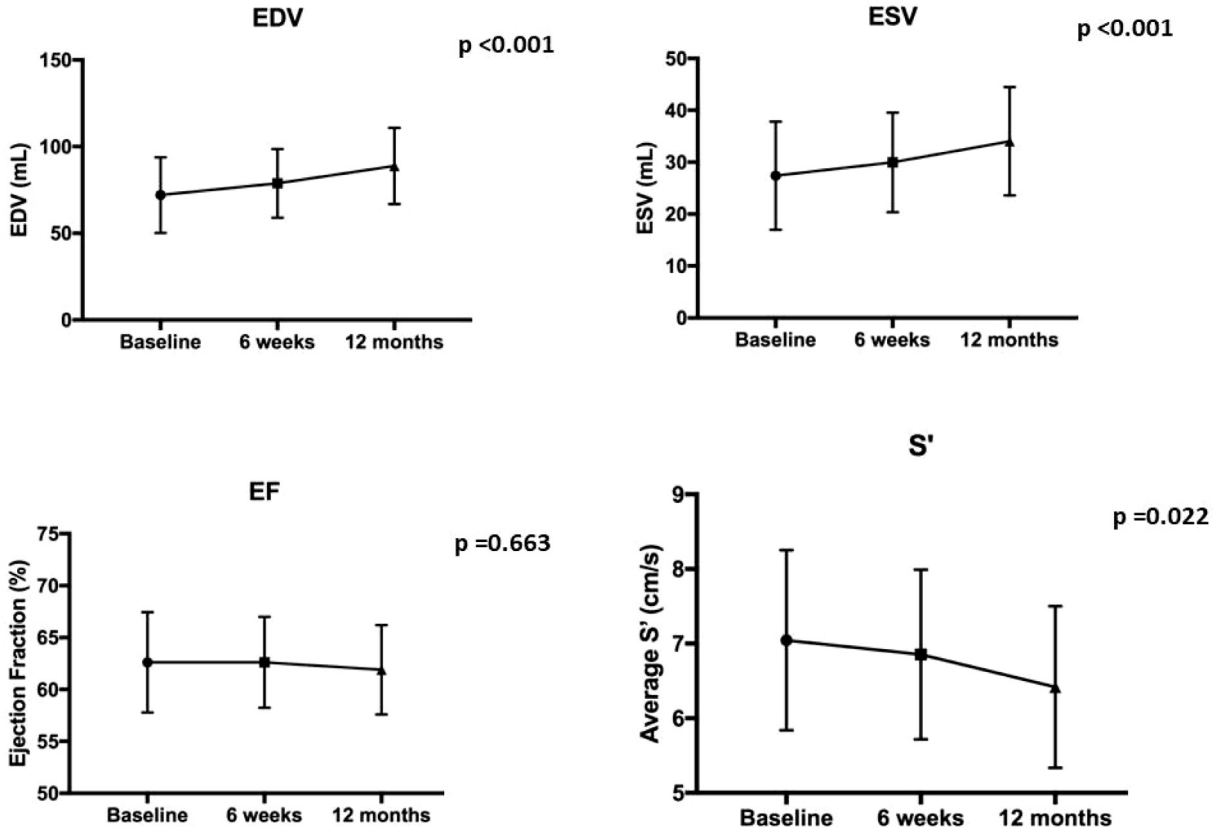

Fig. 1. Time course of changes in LV EDV, ESV, EF, and S′. There was no significant change in the ejection fraction (EF) over time. A reduction in the average S′ velocity was noted over the follow-up period. EDV = end diastolic volume, ESV = end systolic volume, EF = ejection fraction, S′ = average S′ velocity.

nificantly higher LV ESV and lower LVEF compared to those who demonstrated no change or some degree of GLS recovery at either the early or 12-month follow-up time points. This suggests that abnormalities of cardiac function that are observed early (within 6 weeks after RT), continue to be observed 12 months after RT and that these changes may not be detected using conventional indices of LV function including LVEF. Also, these changes are not determined by the initial change in GLS or baseline radiation dose, underscoring the importance of ongoing follow-up and surveillance for cardiac dysfunction in this group of patients.

A statistically significant increase in the LV EDV and ESV was seen from baseline to 12 months in our study. Due to the simultaneous increase in both LV systolic and diastolic volumes over time, no net change in LVEF was observed. This is consistent with the early follow-up data from our group [14], and also similar to data from a recently published prospective study [19]. There was however, a statistically significant reduction in the average S′ value at 12 months, though the absolute S′ velocity was within the normal range.

This is only the second study to investigate the 12-month effects of RT on LV systolic and diastolic function, in particular using contemporary techniques of 2D strain echocardiography. We previously demonstrated that there was a significant reduction in GLS as early as 3 to 4 weeks after commencement of RT that

Table 3
LV volumes and ejection fraction in patients with persistently reduced GLS versus those without.

	Persistent drop in GLS at each time point (n = 16) Mean ± SD	Unchanged or improved GLS (n = 17) Mean ± SD	P value
Biplane EDV (mL)	97 ± 25	83 ± 14	0.056
Biplane ESV (mL)	39 ± 12	30 ± 5	0.006
Ejection Fraction (%)	60 ± 4	64 ± 4	0.005

Abbreviations: EDV = end diastolic volume; ESV = end systolic volume; GLS = global longitudinal strain.

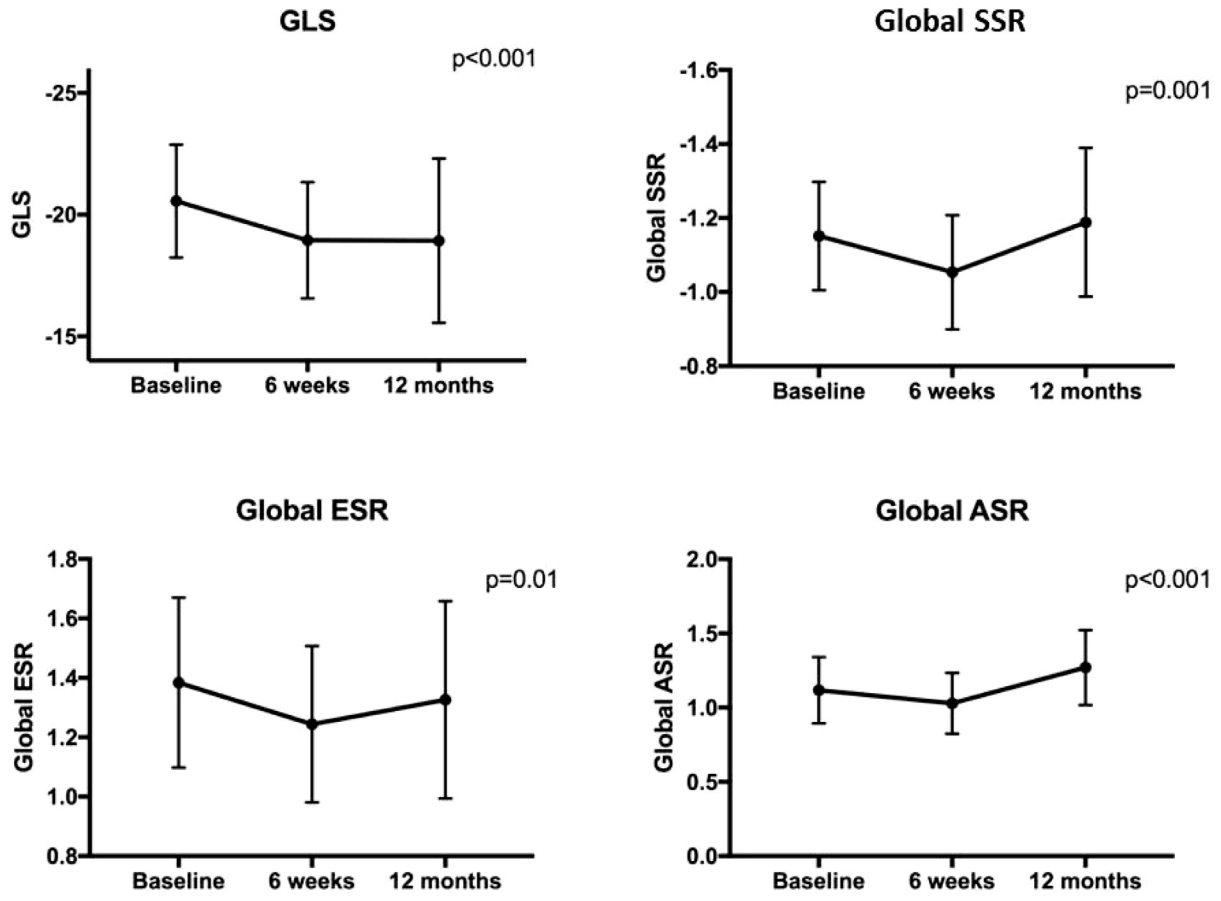

Fig. 2. Time course of changes in strain parameters. There was a statistically significant reduction in the global longitudinal strain (GLS), which persisted at 12 months. There was an early reduction in the global systolic strain rate (SSR), early diastolic strain rate (ESR), and late diastolic strain rate (ASR), with subsequent improvement at 12-month follow-up.

persisted to 6 weeks [14], despite preserved LVEF. This current study demonstrates that the reduction in GLS persists at one year. This finding is consistent with that of Erven et al [20] who noted significant GLS reduction up to 14 months after RT, albeit in a group of breast cancer patients who had also received chemotherapy. They also demonstrated that no significant change was noted in GLS in patients with right sided breast cancer who received radiation [20].

In addition, we observed that the most marked reduction in GLS occurred in the first 6 weeks post-RT. This may be explained by the underlying pathophysiology of RT-induced heart disease. Early events post-RT include myocyte injury and loss of endothelial cells with consequent inflammation and vascular damage [21], which may in part explain the early impaired myocardial deformation. Eventually, RT-induced fibrosis occurs as a reparative response of the heart tissue to injury of the microvascular system [22,23]. The persistently low GLS at 12-month follow-up may reflect this rather than the acute changes due to inflammatory tissue response to RT.

We did not observe a significant change in circumferential strain 6 weeks post-RT [14], and hence circumferential strain was not analysed in this study. Radial strain was also not measured as it has shown significant intra- and inter observer variability [24,25], limiting its clinical utility currently.

With traditional parameters of diastolic function there was a significant increase in peak A velocity with a consequent reduction in the mean E/A ratio at 12-month follow-up. This was in contrast to another younger cohort with less cardiovascular risk factors, where no significant change was noted [20].The global E-Sr, a measure of diastolic dysfunction was significantly reduced at 12-month follow-up, a finding consistent with previous reports [14,15]. In contrast, the global A-Sr was significantly increased at 12 months. This, similar to increase in peak A velocity with reduced E/A ratio, can be explained as a compensatory mechanism: the reduction in early diastolic LV relaxation being balanced by a compensatory increase in late diastolic atrial contractile function [26]. Whilst transmitral flow is load dependent, given the persist

reduction in global E-Sr at12 months, the reduced E/A ratio likely reflects more persistent underlying diastolic changes at 12 months.

We have previously shown a modest correlation between GLS and V30 as well as between GLS and mean heart dose [14] at 6 weeks [15]. Nevertheless, we were unable to demonstrate a difference in radiation dose between the group with a >10% reduction in GLS. However, comparisons comprised of small subgroups of patients, and may suggest that factors apart from radiation dose may contribute. Darby and colleagues have demonstrated that adverse outcomes correlated with radiation dose, but additionally also patient age and associated cardiovascular risk factors [6].

What is most striking about our data is the fact that significant reductions in GLS persist even at 12 months. The reduction in GLS occurred most significantly 6 weeks post-RT, with modest correlation between cardiotoxicity as quantified by the radiation dose, and reduction in GLS observed at this time-point. However, this may in part be due to the inflammatory response to RT, likely to be RT dose dependent. Over 12 months, ventricular remodelling is likely to have occurred, and additionally, improvement in the non-specific local inflammatory response to RT, with possible improvement in GLS. As our sample size was relatively small, we were unable to identify clearly defined predictors of a persistently low GLS at 12-month follow-up.

There were no pericardial effusions or overt increases in pericardial thickening noted in the study patients at any time point. However, we acknowledge that this study had a small number of patients. Pericardial changes, although occasionally seen as an acute effect post radiation, is typically a longer term complication.

In terms of long-term clinical relevance, subclinical cardiac dysfunction has been shown to have long-term adverse outcomes in other patient groups [27,28]. A recent study in breast cancer patients treated with chemotherapy showed that a reduction in GLS of >15% may be of clinical significance [29], and such reductions in GLS are considered indicative of subclinical myocardial damage, as outlined in an expert consensus document [30]. Benefits of early intervention in patients with subclinical cardiac dysfunction have been reported; breast cancer patients with GLS reductions of $\geq -11\%$ after trastuzumab demonstrated improvement in LVEF 6 months after treatment with beta blocker therapy [31]. However, with currently available data, no definitive recommendations are currently in place for the treatment of subclinical cardiac dysfunction in the setting of radiotherapy or chemotherapy [30].

In conclusion, although most marked immediately following RT, abnormalities of cardiac systolic and diastolic function using strain analysis are evident 12 months after completion of RT, whilst conventional indices such as LVEF show no significant change. Ventricular remodelling continues to occur with persistent increase in LV EDV and ESV, albeit with gradual improvement in strain rate. Persistent GLS reductions observed, correlated with greater LV remodelling. Longer term prospective studies are required in larger patient groups to determine the prognostic value of early alteration in GLS as a marker for future adverse cardiac events in this group of patients.

Limitations

The small sample size was a major limitation of this study. However, despite this, the strain analysis demonstrated persistent reduction in GLS at 12 months. Specific hormone therapy may additionally alter GLS; however, subgroup analysis of those who received hormone therapy versus those that did not, demonstrated no significant differences between groups.

Furthermore, we did not observe differences in radiation dose between the subgroup with persistent changes in GLS at 12 months; however, this may represent a beta error due to a relatively small sample size.

As the follow-up in this study was limited to 12 months, and adverse outcomes consequent to radiation therapy are seen beyond this period, a larger study, with longer duration of follow-up would be required to validate our current observations and to determine its impact on long-term adverse outcomes. Finally, we did not evaluate the impact of radiation dose on specific cardiac structures such as the coronary arteries. However, radiation-induced vasculopathy is known to occur late after radiation exposure [32].

Cardiac magnetic resonance imaging was not performed in these patients to specifically evaluate myocardial oedema. However, previous histopathological studies have reported myocardial oedema as an acute effect post radiation therapy.

Conflict of interest

All authors have no conflicts of interest to declare.

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