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ORIGINAL PAPER

Radiotherapy-induced global and regional differences in early-stage left-sided versus right-sided breast cancer patients: speckle tracking echocardiography study

Suvi Sirkku Tuohinen[1] · Tanja Skyttä[2] · Tuija Poutanen[3] · Heini Huhtala[4] · Vesa Virtanen[1] · Pirkko-Liisa Kellokumpu-Lehtinen[2] · Pekka Raatikainen[5]

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Abstract Radiotherapy (RT) to the thoracic region increases late cardiovascular morbidity and mortality. The impact of breast cancer laterality on cardiac function is largely unknown. The aim of this prospective study was to compare RT-induced changes in left-sided and right-sided breast cancer patients using speckle tracking echocardiography (STE). Sixty eligible patients with left-sided breast cancer and 20 with right-sided breast cancer without chemotherapy were evaluated prospectively before and early after RT. A comprehensive echocardiographic examination included three dimensional measurements and STE of the left ventricle (LV). The global longitudinal strain (GLS) was reduced from -18.3 ± 3.1 to $-17.2 \pm 3.3\%$ ($p = 0.003$) after RT in patients with left-sided breast cancer. Similarly, regional analysis showed a reduction in the apical strain from -18.7 ± 5.3 to $-16.7 \pm 4.9\%$ ($p = 0.002$) and an increase in basal values from -21.6 ± 5.0 to $-23.3 \pm 4.9\%$ ($p = 0.024$). Patients with right-sided breast cancer showed deterioration in basal anterior strain segments from -26.3 ± 7.6 to $-18.8 \pm 8.9\%$ ($p < 0.001$) and in pulsed tissue Doppler by 0.825 [0.365, 1.710] cm/s ($p < 0.001$). In multivariable analysis, the use of aromatase inhibitor ($\beta = -2.002$, $p = 0.001$) and decreased LV diastolic volume ($\beta = -0.070$, $p = 0.025$) were independently associated with the decrease in GLS. RT caused no changes in conventional LV systolic measurements. RT induced regional changes corresponded to the RT fields. Patients with left-sided breast cancer experienced apical impact and global decline, whereas patients with right-sided breast cancer showed basal changes. The regional differences in cardiac impact warrant different methods in screening and in the follow-up of patients with left-sided versus right-sided breast cancer.

Keywords Speckle tracking · Breast cancer · Radiotherapy · Laterality

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✉ Suvi Sirkku Tuohinen
suvi.tuohinen@fimnet.fi

[1] Heart Center Co., Heart Hospital, Tampere University Hospital and School of Medicine, University of Tampere, PO Box 2000, 33521 Tampere, Finland

[2] Department of Oncology, Tampere University Hospital and School of Medicine, University of Tampere, Tampere, Finland

[3] Department of Pediatrics, Tampere University Hospital and School of Medicine, University of Tampere, Tampere, Finland

[4] School of Health Sciences, University of Tampere, Tampere, Finland

[5] Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

Introduction

Breast cancer is the most common cancer in women worldwide [1]. Radiotherapy (RT) reduces local breast cancer relapses and disease-related mortality but doubles late cardiovascular morbidity and mortality [2–4]. Breast cancer laterality has major importance. Patients with left-sided breast cancer have a 1.3 to 1.6-fold relative risk of cardiovascular complications 10 years after RT, compared with right-sided breast cancer patients [1, 4–6]. However, the RT-induced cardiac impact is more associated with the cardiac radiation exposure rather than breast cancer laterality [5], and the increase in coronary events has been estimated to vary from 4 to 7.4% per Gray (Gy) of the mean

heart dose [1, 5]. The average cardiac exposure of patients with right-sided breast cancer has been estimated at 3.3 Gy (0.4–6 Gy) [7, 8], resulting in at least a 1.6–3.0% increase in risk for coronary events. The majority of the studies of RT-induced cardiac changes in breast cancer patients have focused on patients with left-sided breast cancer, and knowledge of the changes among patients with right-sided breast cancer is limited.

Myocardial deformation imaging in echocardiography has major advantages over conventional measurements. It is more sensitive for detecting subtle changes in earlier phases than conventional functional measurements over wide variety of pathologies [9, 10]. Colour strain measurements have detected changes in myocardial deformation in regions receiving radiation doses >3 Gy [11]. In speckle tracking echocardiography (STE) analysis, global longitudinal strain (GLS) decreased after RT in left-sided breast cancer patients [9]. However, the early manifestations after RT in patients with right-sided breast cancer have not been well characterized. The aim of this study was to illuminate the differences induced by RT exposure laterality in the early phase after adjuvant RT in breast cancer patients using the STE method.

Materials and methods

Patient selection

A total of 80 eligible female patients with early-stage breast cancer were included in this single-centre, prospective clinical study between July 2011 and November 2013. Sixty of them had left-sided breast cancer, and 20 had right-sided breast cancer. Following breast cancer surgery, all patients received adjuvant conformal three dimensional (3D) RT. None of these early stage breast cancer patients received chemotherapy. Other exclusion criteria were age under 18 or over 80 years, other malignancies, pregnancy or breast feeding, acute myocardial infarction within 6 months, symptomatic heart failure (NYHA 3–4), dialysis, permanent anticoagulation and severe psychiatric disorders. Patients with atrial fibrillation, left bundle branch block, permanent pacemaker and severe lung disease were also excluded to improve the quality of echocardiographic imaging. The protocol was approved by the local institutional board of ethics (R10160), and all of the participants provided written informed consent before enrolment.

Radiotherapy

The RT protocol used in this study has previously been described in detail [12]. In brief, 3D computed tomography treatment planning and contouring were performed in all of the patients (Fig. 1). The treatment schedule was either 50 Gy in 2 Gy fractions (standard) or 42.56 Gy in 2.66 Gy fractions (hypofractionated). An additional boost of 16 Gy in 2 Gy fractions to the tumour bed was used, if clinically indicated. Doses were calculated using the anisotropic analytical algorithm, and dose-volume histograms for different structures were generated (Table 1).

Cardiac examinations

Patients were examined 6 ± 8 days prior to RT and 1 ± 1 days after RT treatment with median time interval between the studies 38 days (19–93 days). Blood samples for high sensitivity troponin T (hsTnt) and pro-B-type natriuretic peptide (proBNP) were collected at the baseline,

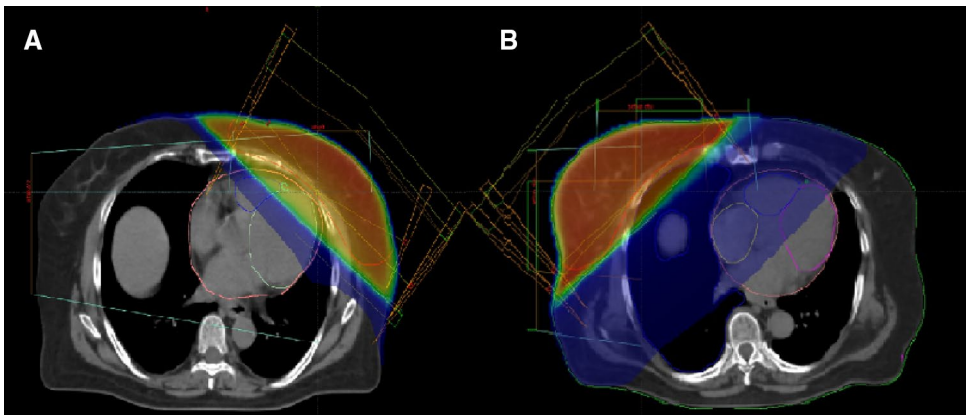

Fig. 1 3D CT radiotherapy treatment planning. On the left side (**a**), treatment fields for left-sided breast cancer are illustrated, with *blue* colouring marking fields receiving a 2 Gy dose and *yellow* to *red* colouring illustrating increasing radiation doses. **b** The typical RT field in patients with right-sided breast cancer, here with the *blue* colouring demonstrating fields receiving 0.5 Gy radiation doses. Manually depicted heart contouring is also shown for the whole heart, for the left ventricle and for the right ventricle

Table 1 Radiation doses to the different cardiac structures in Grays

	Left-sided breast cancer		Right-sided breast cancer	
	n = 60		n = 20	
	Median	[Min, Max]	Median	[Min, Max]
Mean heart	3.1	[0.7, 6.8]	0.6	[0.3, 4.8]
Peak heart	47.0	[5.8, 64.2]	4.5	[2.5, 19.1]
Mean LV	4.4	[0.8, 12.3]	0.1	[0.0, 3.3]
Peak LV	45.8	[4.5, 63.8]	0.4	[0.2, 5.2]

LV left ventricle

once during treatment and at the end of RT treatment. Comprehensive echocardiography was performed, and a 12-lead electrocardiogram (ECG) was obtained at each visit.

All echocardiographic examinations were performed by the same cardiologist (SST) using a commercially available cardiac ultrasound machine (Philips iE33 ultrasound system, Bothell, WA, USA) and a 1–5 MHz matrix-array X5-1 transducer. The imaging was acquired at rest, and Doppler recordings were acquired at end-expiration. The patients were in the left lateral decubitus position. A simultaneous superimposed ECG was used throughout the studies. The images were stored on an external hard drive for off-line analysis (Philips Qlab, Bothell, WA, USA). For STE analysis, three apical clips (four chamber, two chamber and three chamber) and three parasternal clips (short axis clips at the level of the mitral valve, the papillary muscle level and the apex) of the left ventricle (LV) were acquired over three cycles. Care was taken to optimize the visualization of the LV muscle throughout the cycles, aiming at a frame-rate of 60–90 Hz. Adequate tracking was controlled by visual inspection, and reanalysis was performed if necessary. Segments with repeated inadequate tracking were excluded from the final results. Regional results were calculated as average values from the segments located correspondingly.

Statistical analysis

The data are reported as means and standard deviations for normally distributed variables and as medians with ranges for other continuous variables. Differences between the groups in the baseline characteristics were tested with Student's *t*-test for continuous variables and with Fisher's exact test for categorical variables. The change from baseline to after RT was analysed with the paired samples *t*-test for normally distributed variables and with Wilcoxon's signed rank test for variables with skewed distribution. Categorical variables were analysed with the Chi square test/Fisher's exact test. Associations of the variables with the changes in STE values were calculated with Pearson's correlation or with Spearman's correlation for non-normally distributed variables. The differences in GLS changes between patients who smoked or did not smoke and other baseline diagnoses or medications were tested with Student's *t*-test. Binary logistic and linear regression analysis were used to test univariate associations for categorical and continuous variables. Stepwise linear regression analysis was used to test multivariable associations with GLS changes and tested parameters are shown in the corresponding tables. The reproducibility of the STE data was tested in 20 healthy volunteers from blinded data with intraclass correlation. All of the tests were two-sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software, version 23 for Windows (Armonk, NY, USA).

Results

General characteristics

The mean age of the study group was 63 ± 6 years. Thirty-three patients (41%) had no other concurrent disease. The most common underlying diseases included hypertension (44%), hypercholesterolaemia (23%) and hypothyroidism (13%). Twenty patients (25%) were current or ex-smokers. Fifty patients (63%) had a body mass index (BMI) >25 cm/m^2. Detailed baseline characteristics of the patients in each group are shown in Table 2.

Speckle tracking analysis

Patients with left-sided breast cancer

Patients with left-sided breast cancer displayed changes in global strain of $1.1 \pm 2.7\%$ ($p = 0.003$), and a more than 10% decrease from the baseline GLS value was experienced by 17 patients (28%). Regional analysis showed reductions in apical values of $2.0 \pm 4.5\%$ ($p = 0.002$) and apex values of $1.9 \pm 4.4\%$ ($p = 0.003$) and an increase in basal strain values of $1.7 \pm 5.4\%$ ($p = 0.024$); for details, see Table 3. Circumferential analysis and systolic strain rate analysis (see Supplementary Tables 1, 2) were less sensitive for detecting RT-induced changes in patients with left-sided breast cancer. In multivariable analysis, the changes in the apical segments were independently associated with prolonged apical rotation time ($\beta = 0.012$, $p = 0.011$) and with increasing LV mass ($\beta = -0.076$, $p = 0.024$). In addition, increased myocardia reflectivity (sccIBS) had an independent association with decreasing basal strain values ($\beta = 0.293$, $p = 0.045$).

Table 2 Baseline characteristics of the study population

	Left-sided breast cancer n = 60		Right-sided breast cancer n = 20		p
	Mean	SD	Mean	SD	
Age (years)	63.6	6.8	62.9	4.7	0.657
Systolic blood pressure (mmHg)*	144	19	150	20	0.287
Diastolic blood pressure (mmHg)*	79	12	79	12	0.918
Body mass index (kg/m^2)[a]	26.3	[24.1, 29.9]	26.6	[24.7, 30.0]	0.567
	n	(%)	n	(%)	
Smoking					
Current	9	15	2	10	0.722
Previous	7	12	2	10	1.000
Prior diagnosis[b]					
Hypertension	22	37	13	65	***0.038***
Diabetes mellitus	4	7	3	15	0.358
Hypercholesterolaemia	14	23	4	20	1.000
Hypothyroidism	7	12	3	15	0.705
Coronary artery disease					
Significant valvular abnormality	3	5	2	10	0.594
Medical treatment					
Beta blockers	7	12	5	25	0.163
Calcium channel blockers	4	7	4	20	0.102
ACE inhibitors/ARBs	15	25	10	50	*0.052*
Diuretics	8	13	7	35	***0.047***
Thyroxin	7	12	3	15	0.705
Nitrates	1	2	0	0	1.000
Aspirin	7	12	3	15	0.708
Statins	12	20	4	20	1.000
Oral diabetes medications	4	7	3	15	0.358
Aromatase inhibitors	22	37	8	40	0.796
Tamoxifen	2	3	4	20	***0.032***

Statistically significant p-values ($p < 0.05$) are in bold italics and values with tendency to statistically significance with italics (p-value between 0.05–0.10)

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker

[a]Non-normal distribution, reported as median, [Q_1, Q_3]

[b]Medication-requiring state

*Measured at the first visit

Patients with right-sided breast cancer

No significant change in GLS was observed in patients with right-sided breast cancer. However, segmental analysis revealed a decrease in the basal anterior segment in the strain analysis from -26.2 ± 7.8 to $-17.9 \pm 8.2\%$ ($p < 0.001$) and in the pulsed tissue Doppler analysis from 7.1 [6.1, 7.7] to 5.6 [5.3, 6.5] cm/s ($p < 0.001$) (Fig. 2). In multivariable analysis, delayed basal rotation time ($\beta = -0.035$, $p = 0.020$) was independently associated with changes in strain. Hypertension ($\beta = -1.272$, $p = 0.009$) and change in LV end diastolic diameter ($\beta = 0.042$, $p = 0.024$) had independent associations with the decrease in the anterior pulsed tissue Doppler value.

Multivariate analysis for overall GLS changes

The results of the correlation and multivariable analyses for GLS changes are displayed in Table 4. In multivariable analysis, the use of aromatase inhibitors (AIs) ($\beta = -2.002$, $p = 0.001$) and a decrease in LV diastolic volume had independent associations with a reduction in GLS ($\beta = -0.070$, $p = 0.025$). They explained 23% of the total GLS change after RT.

Table 3 Longitudinal systolic speckle tracking and pulsed tissue Doppler measurements

	Left-sided breast cancer n = 60					Right-sided breast cancer n = 20				
	Baseline		After RT		p	Baseline		After RT		p
Speckle tracing measurements										
Longitudinal strain (%)	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
GLS	−18.3	±3.1	−17.2	±3.3	***0.003***	−16.9	±3.8	−17.2	±2.8	0.577
Basal	−21.6	±5.0	−23.3	±4.9	***0.024***	−21.1	±4.3	−20.3	±4.2	0.576
Mid	−19.4	±4.6	−17.7	±5.9	***0.039***	−17.6	±5.3	−18.5	±5.0	0.489
Apical	−18.7	±5.3	−16.7	±4.9	***0.002***	−16.5	±5.6	−18.0	±4.2	0.159
Apex	−18.3	±5.1	−16.5	±4.8	***0.003***	−16.0	±5.7	−17.1	±4.4	0.334
Anterior	−18.2	±4.3	−17.6	±4.4	0.277	−18.5	±4.4	−16.9	±4.9	*0.089*
Anteroseptal	−19.2	±3.9	−18.5	±4.7	0.281	−17.7	±4.5	−18.7	±5.1	0.374
Inferoseptal	−21.2	±3.7	−20.2	±4.0	0.110	−19.1	±3.8	−20.2	±4.0	0.229
Inferior	−20.3	±4.0	−19.6	±4.8	0.264	−19.8	±4.7	19.6	±2.8	0.854
Inferolateral	−20.2	±4.4	−19.1	±4.5	0.122	−18.6	±4.3	−19.0	±3.4	0.704
Anterolateral	−20.5	±3.6	−20.6	±4.2	0.874	−19.3	±5.0	−20.2	±3.5	0.528
Longitudinal strain rate (1/s)	Median	[Q1, Q3]	Median	[Q1, Q3]		Median	[Q1, Q3]	Median	[Q1, Q3]	
Global	−1.251	[−1.453, −1.107]	−1.296	[−1.450, −1.108]	0.393	−1.324	[−1.531, −1.183]	−1.366	[−1.501, −1.169]	0.823
Basal	−1.455	[−1.752, −1.171]	−1.618	[−1.869, −1.367]	***0.006***	−1.559	[−1.828, −1.380]	−1.521	[−1.859, −1.379]	0.837
Mid	−1.256	[−1.642, −1.095]	−1.381	[−1.602, −1.087]	0.237	−1.471	[−1.698, −1.160]	−1.354	[−1.665, −1.151]	0.794
Apical	−1.093	[−1.295, −0.950]	−1.075	[−1.241, −0.924]	0.201	−1.110	[−1.293, −0.993]	−1.211	[−1.321, −0.963]	0.940
Apex	−1.050	[−1.218, −0.895]	−0.991	[−1.148, −0.870]	0.174	−1.104	[−1.226, −0.940]	−1.159	[−1.369, −0.964]	0.970
Anterior	−1.150	[−1.518, −0.986]	−1.204	[−1.589, −0.999]	0.201	−1.273	[−1.543, −1.137]	−1.261	[−1.467, −1.072]	0.227
Anteroseptal	−1.252	[−1.549,−1.071]	−1.231	[−1.460,−1.092]	0.521	−1.317	[−1.367,−1.009]	−1.312	[−1.637,−1.178]	0.211
Inferoseptal	−1.189	[−1.314, −1.076]	−1.206	[−1.401, −1.101]	0.891	−1.324	[−1.601, −1.178]	−1.363	[−1.543, −1.131]	0.794
Inferior	−1.313	[−1.543, −1.135]	−1.391	[−1.717, 1.157]	0.717	−1.445	[−1.673, −1.258]	−1.434	[−1.717, −1.134]	0.349
Inferolateral	−1.310	[−1.848, −1.063]	−1.366	[−1.613, 1.193]	0.615	−1.498	[−1.713, −1.181]	−1.386	[−1.672, −1.169]	0.981
Anterolateral	−1.313	[-1.801, −1.074]	−1.324	[−1.591, −1.119]	0.402	−1.487	[−1.633, −1.154]	−1.368	[−1.632, −1.223]	0.841
Pulsed tissue Doppler measurements (cm/s)										
Septal	6.6	[6.2–7.4]	6.7	[5.9–7.8]	0.616	6.6	[6.0–7.7]	6.7	[6.0–7.7]	0.498
Lateral	7.2	[6.1–8.4]	7.0	[5.9–8.3]	0.224	7.4	[6.1–8.4]	7.0	[6.2–7.4]	0.227
Posterior	7.8	[7.0–8.6]	7.6	[6.7–8.6]	0.099	7.8	[7.3–8.7]	7.6	[6.7–8.4]	0.355
Anterior	6.2	[5.5–7.5]	5.9	[5.2–7.1]	***0.026***	7.1	[6.1–7.7]	5.6	[5.3–6.5]	***<0.001***

Statistically significant p-values ($p < 0.05$) are in bold italics and values with tendency to statistically significance with italics (p-value between 0.05–0.10)

GLS global longitudinal strain

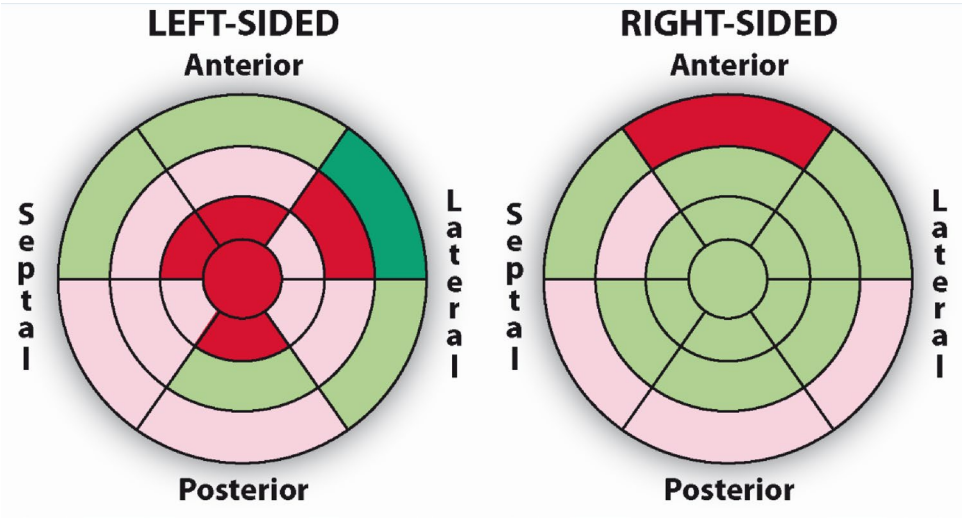

Fig. 2 Segmental changes in longitudinal strain after radiotherapy. The *green* colour shows segments with increasing function and red those with declining function. The *darker green* and *red* colours show segments with statistically significant changes ($p < 0.05$). Patients with left-sided breast cancer are shown on the left side and patients with right-sided breast cancer on the right side

Table 4 Factors associated with GLS changes after radiotherapy

	Correlations					Multivariable analysis[a]		
	r	p				β	SE (β)	p
Age (years)	−0.237	***0.043***						0.549
Mitral E-wave change (cm/s)	−0.300	***0.010****						0.420
LV mass change (3D) (g)	−0.309	***0.012***						0.502
LVDV change (3D) (ml)	−0.292	***0.018***				−0.070	0.025	***0.007***
Ef change (3D) (%)	−0.250	***0.047***						0.457
Mean heart (Gy)	−0.077	0.516						0.790
	GLS change[b]							
	With		Without		p			
	Mean	SD	Mean	SD				
Aromatase inhibitor	−2.0	0.5	0.0	2.7	***0.001***	−2.002	0.579	***0.001***
Smoking	−1.5	2.6	−0.5	2.8	0.173			0.091
Valvular abnormality	−3.2	3.7	−0.5	2.6	***0.037***			0.891
Patient group (left)	−1.1	2.7	0.4	2.8	***0.040***			0.137
Hypertension	−1.0	2.7	−0.5	2.8	0.511			0.910
Diabetes	−1.7	2.6	−0.6	2.8	0.323			0.562

Statistically significant p-values ($p < 0.05$) are in bold italics

GLS global longitudinal strain, *LV* left ventricle, *3D* three-dimensional, *LVDV* LV end-diastolic volume, *Ef* ejection fraction, *Mean heart* mean radiation dose to the whole heart, *Patient group (left)* patients with left-sided breast cancer

*Spearman's correlation; Pearson's correlation for others

[a]The analysis is performed with linear forward stepwise regression analysis

[b]The given number under definition 'with' presents GLS decline with patients using Aromatase inhibitor, patient smoking, with significant valvular lesions, patients with left-sided breast cancer and patients with hypertonia and diabetes, respectively. In the column 'without' the GLS change after RT in patients without these conditions is shown

Conventional echocardiographic measurements

In the whole group, the LV myocardial mass derived from 3D imaging increased from 105 ± 21 to 109 ± 21 g ($p = 0.010$). On two-dimensional imaging, increases were found in relative wall thickness, and in septal and posterior wall thickness: $p = 0.002$, 0.001 and $p = 0.001$, respectively. The changes in diastolic function were found to result in

Table 5 Conventional echocardiography measurements

	Left-sided breast cancer n = 60					Right-sided breast cancer n = 20				
	Baseline		After RT		p	Baseline		After RT		p
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
LVEDD (mm)	45.1	±4.1	44.7	±3.9	0.157	43.7	±4.6	43.8	±3.9	0.920
LVEDS (mm)	30.3	±3.5	30.0	±3.6	0.455	29.7	±3.2	29.3	±3.4	0.428
IVS (mm)*	10.0	[9.0, 11.0]	10.0	[9.2, 11.0]	***0.009***	10.0	[8.9, 11.3]	10.6	[9.0, 11.9]	***0.018***
PW (mm)*	10.0	[9.0, 10.8]	10.2	[9.7, 11.0]	***0.003***	10.0	[9.1, 11.1]	10.4	[9.9, 11.5]	0.251
RWT*	0.42	[0.40, 0.49]	0.46	[0.43, 0.50]	***0.003***	0.45	[0.41, 0.54]	0.46	[0.43, 0.54]	0.411
LVEDV (ml)	99	±19	95	±18	***0.038***	97	±26	98	±25	0.832
LVEDS (ml)	40	±9	39	±11	0.345	39	±12	41	±11	*0.051*
LVED mass (g)	105	±20	108	±21	***0.012***	106	±23	108	±24	0.483
LV EF (%)	65	±7	65	±7	0.810	64	±10	66	±6	0.616
IVRT (ms)	104	±25	110	±22	*0.082*	111	±22	111	±14	0.981
Mitral inflow E (cm/s)*	71	[64, 83]	67	[58, 79]	***0.031***	76	[63, 89]	67	[61, 80]	*0.067*
Mitral inflow a (cm/s)	78	±20	75	±15	*0.055*	78	±14	78	±21	0.871
Mitral inflow dt (ms)*	230	[203, 260]	239	[207, 271]	0.214	211	[180, 240]	238	[198, 274]	***0.015***
LV E/e' ratio*	8.9	[7.1, 11.1]	9.0	[7.1, 10.0]	0.183	10.1	[7.6, 12.4]	9.3	[7.5, 11.7]	0.970
RV basal dimension (mm)	34.2	±5.0	33.6	±4.5	0.340	34.3	±6.0	33.6	±5.7	0.522
TAPSE (mm)	24.2	±4.0	22.3	±4.0	***<0.001***	23.4	±5.4	22.5	±5.2	0.141
RV s' (cm/s)	11.6	[10.3, 13.2]	11.1	[10.2, 13.2]	0.099	13.4	[10.7, 14.7]	12.2	[10.9, 14.1]	0.681
TR gradient (mmHg)	21.5	±5.6	21.4	±4.7	0.677	23.0	±6.9	20.6	±6.1	***0.025***

Statistically significant p-values ($p < 0.05$) are in bold italics and values with tendency to statistically significance with italics (p-value between 0.05–0.10)

LVEDD and *LVEDS* left ventricular end-diastolic and end-systolic diameters, *IVS* and *PW* interventricular septum and posterior thicknesses at the end-diastole, *RWT* relative wall thickness, *LVEDV, LVESV* and *LVED mass* left ventricular end-diastolic and end-systolic volumes and end-diastolic mass derived from the three dimensional acquisition, *EF* ejection fraction, *IVRT* isovolumetric relaxation time, *dt* declaration time, *E/e' ratio* ratio between mitral inflow E velocity and averaged pulsed Doppler velocity derived from septal, lateral, anterior and posterior walls, *RV* right ventricle, *TAPSE* tricuspidal annular plane systolic excursion, *RV s'* the systolic velocity of pulsed tissue Doppler recording derived from RV lateral basal region, *TR gradient* tricuspid regurgitation maximal gradient

*Median and [Q_1, Q_3]

decreases in mitral inflow E-wave and prolongation of the E-wave's declaration time: p = 0.005 and 0.018, respectively. The changes were more prevalent in left-sided breast cancer patients; Table 5.

Electrocardiogram and biochemical markers

RT induced minor ECG changes in 44 patients (55%). The most typical changes were T-wave inversions or reductions in leads V1-4, aVL and I. ECG changes were more common in patients with left-sided breast cancer than in patients with right-sided breast cancer (39 vs. 5 patients) (p = 0.003).

The baseline and the highest (Q_1, Q_3) hsTnt values were 4 (4, 15) and 5 (4, 15) ng/l (p = 0.006) in patients with left-sided breast cancer and 4 (4, 33) and 5 (4, 20) ng/l (p = 0.287) in patients with right-sided breast cancer, respectively. More than 30% increase in hsTnt was found in 14 patients and one patient among left-sided and right-sided patients, respectively (p < 0.001).

In patients with left-sided breast cancer, the baseline proBNP value was 59 (14, 824) ng/l with an increase to 88 (15, 1101) ng/l (p < 0.001). The respective values were 92 (12, 160) and 86 (24, 261) ng/l (p = 0.809), in patients with right-sided breast cancer. A more than 30% increase in proBNP value was observed in 32 left-sided and four right-sided patients (p = 0.014).

Reproducibility

The longitudinal measurements showed generally higher reproducibility than the circumferential measurements, and

the strain values were higher than the strain rate values. In the regional analysis, the apical regions seemed to be more reproducible than the basal regions in longitudinal measurements, whereas in the circumferential analysis, the anterior regions were more reliable than the posterior regions. For detailed analyses, see Supplementary Table 3.

Discussion

In this prospective study, STE analysis could detect differences in the global and regional changes in myocardial function in the early stage after adjuvant RT in patients with left-sided versus right-sided breast cancer. RT-induced changes in patients with right-sided breast cancer have not been previously reported. Due to different locations of the changes in patients with left-sided and right-sided breast cancer, the late stage complications might differ according to the breast cancer laterality.

RT-induced changes in tissues

Radiation produces sequential, time-dependent changes in tissue. The first phase consists of inflammation with oedema, extravasation and activation of the coagulation cascade [13, 14]. It is generally believed that a complex cascade is launched during the early phase and results in progressive fibrotic changes over years to decades after RT treatment [14]. The inflammatory phase subsides to a latent phase within 2 days after RT exposure [13]. The latent phase is characterized by capillary damage caused by endothelial injury and thrombotic lesions [13, 14]. The first signs of the fibrotic phase have been found 40–70 days after the completion of RT treatment [13]. In the heart, the clinical late sequelae appear 5–15 years after RT treatment and consist of wide variety of changes [3, 15]. The most lethal changes are coronary lesions, typically of a fibrotic nature with ostial and anterior locations [3, 15]. Myocardial changes can produce thickening of the LV walls resulting in filling problems and restrictive cardiomyopathy [3]. Valvular stenosis and regurgitation, arrhythmia and conduction disturbances and pericardial constriction are also well-known complications after thoracic RT treatment [3, 15]. Our patients were re-examined within 3 days after the RT treatment, well within the inflammatory period, though the initial phase of the fibrosis could theoretically have started.

STE changes in patients with left-sided breast cancer

RT induced an apical decline in the LV systolic function in patients with left-sided breast cancer in the present study, which was in concordance with previous studies by Erven and Heggemann [11, 16]. These changes were detectable both in the longitudinal strain and strain rate analyses, as well as at global, regional and segmental levels. The basal regions had a compensatory increase in function. The basal compensation was, however, not sufficient to compensate for the global functional loss, and the patients experienced a decrease in the GLS. Similar findings were reported by Lo [9]. A more than 10% decrease in the GLS is generally considered clinically significant [17], and this change was observed in 28% of our patients with left-sided breast cancer. Other conventional systolic functional LV measurements were not sufficiently sensitive to detect these RT-induced changes.

STE changes in patients with right-sided breast cancer

Patients with right-sided breast cancer received significantly less cardiac radiation. Another main difference was the localization of the RT fields, as shown in Fig. 1. The optimal tangential right-sided RT fields usually do not reach the basis of the LV. However, due to individual anatomy (e.g., large breasts), additional fields were used in some patients to ensure optimal target volume coverage, and a marked variation in LV doses was observed (LV mean 0.0–3.3 Gy). In the LV longitudinal segmental analysis, both strain and pulsed tissue Doppler values decreased in the basal anterior LV myocardium. Because of the small affected area, the global function remained unaffected both in the STE analysis and in the conventional echocardiography measurements. However, in the diastolic parameters, an increase in the declaration time and a tendency towards a decrease in the mitral E-wave were found.

Other RT-induced cardiac changes

Other measurements showed increased thickness in the myocardium on both 2D and 3D echocardiography with a simultaneous decrease in the LV diastolic volume, along with minor changes in diastology, and in TAPSE (tricuspid annular plane systolic excursion). The early inflammatory effect of the RT treatment with extravasation and tissue swelling would be a logic explanation to increased myocardial mass along with the changes in diastology, though the exact mechanism remains speculative in the absence of tissue samples. Furthermore, ECG showed changes in the anterior leads mainly in patients with left-sided breast cancer, corresponding to the anterior location of the RT fields. Moreover, there were slight but statistically significant increases in serum hsTnt and proBNP values in patients with left-sided breast cancer. All of these subtle changes might represent the same subclinical cardiac changes induced by breast cancer adjuvant RT, as observed in the STE analysis.

Clinical implications of the findings in this study

Subclinical cardiac changes precede actual cardiac sequelae, and their presence might indicate greater risk for evolution to radiotherapy-induced heart disease (RIHD). Hence, interest in RT-induced early cardiac changes has emerged, and it is debated whether patients receiving RT in the thoracic regions should be followed up regularly [3]. The early manifestations have not been well characterized, and their detection is considered challenging, even more so for right-sided breast cancer patients. The cardiac radiation dose after left-sided breast cancer RT is higher than that after right-sided breast cancer [7], as also shown in our study. In studies comparing the impact of breast cancer laterality, cardiac mortality and morbidity were higher after left-sided RT [1, 5, 6]. However, the impact of right-sided RT is not negligible. It has been shown that the mean heart radiation dose itself induces an increased cardiac risk, and with a cardiac exposure of 0.3–4.8 Gy, our patients with right-sided breast cancer could face a 2.2–35.5% increased risk of ischaemic heart disease within 5 years [5]. Considering the difference in the location of the RT fields, the cardiac impact after RT and its early lesions might be different in patients with left-sided and right-sided breast cancer. Our study was the first to indicate this decline in systolic function in regions corresponding to the RT fields in patients with right-sided breast cancer, with a clear difference from the changes after left-sided RT in transthoracic echocardiography examination. Considering the screening for early changes, this is a worthwhile fact to notice. Although the GLS has shown promise to be an early and sensitive tool to detect subclinical changes over a wide range of pathologies [10, 17], it might fail to reveal RT-induced cardiac injury in patients with right-sided breast cancer.

The effects of the concurrent endocrine treatment

The impact of the concurrent use of AIs on the GLS decrease after RT was also interesting. Oestrogen has positive effects on cardiac function and recovery [18]. Aromatase is an enzyme regulating the final pathway of oestrogen metabolism. When it is blocked, the tissue level of oestrogen declines. In breast cancer patients, inhibition of this enzyme is used to block oestrogen-induced growth stimulation of cancer tissue. The simultaneous use of AIs during RT has been shown both to sensitize the RT effect and to potentiate RT-induced cardiac functional decline [19, 20]. Similar effects might explain the strong association between the simultaneous use of AIs and a decrease in GLS.

Limitations of our study

The patient population was uniform in many ways, which could limit the application of the results in other patient groups. The echocardiographic studies were performed by a single experienced cardiologist who always used the same equipment, resulting in unique standardized conditions, which might not correspond to general clinical practice. Additionally, the reproducibility was not equally distributed in all of the measured values, which might have influenced the reliability of some of the measurements. Because this study was an observational, non-randomized study with main focus on the group of patients with left-sided breast cancer, the groups with left-sided and right-sided breast cancer were of unequal sizes. Furthermore, the size of the patient population was relatively small, which might limit the clinical implications of the results. Finally, these results showed very short term outcome. Follow-up of this prospectively collected patient population is currently under way to explore the further development of these early cardiac changes.

Conclusion

Our study confirmed the previous findings of global LV functional changes, along with apical impact, after RT in patients with left-sided breast cancer. The basal anterior impact after right-sided RT was a novel finding and indicated that a different approach is needed for the detection of right-sided cancers in screening and follow-up.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest to declare, financial or otherwise.

Ethical approval This study has been approved by the local ethics committee and it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All persons included in this study have given informed consent prior their inclusion in the study.

Research involving animal rights This study does not contain any studies with animals performed by any of the authors.

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