Left Ventricular Speckle Tracking Echocardiography Changes Among Early-stage Breast Cancer Patients Three Years After Radiotherapy

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Abstract. *Background/Aim:* Chest radiotherapy (RT) doubles late cardiac mortality. This study aimed to evaluate the evolution of cardiac changes in speckle tracking echocardiography during a three-year follow-up. *Materials and Methods:* This prospective study included 81 chemotherapy-naïve early-stage breast cancer patients who were evaluated at baseline, immediately after RT and three years after RT. Sixty-one patients had left-sided (LSBC) and 20 right-sided breast cancer (RSBC). *Results:* Global longitudinal strain (GLS) declined from baseline $-18.0 \pm 3.3\%$ to $-17.0 \pm 3.0\%$ ($p=0.015$) at the three-year follow-up examination. A decline over 15% (GLS15) was observed in 19 (27%) patients. GLS15 was independently associated with aromatase inhibitor use ($\beta=-1.977$, $p=0.001$). In regional analysis, patients with LSBC had apical strain decline by $3.2 \pm 5.5\%$ ($p<0.001$) and patients with RSBC showed basal rotation decline by 1.8° (-0.2° , 3.8°) ($p=0.030$). *Conclusion:* Even contemporary RT induced progressive global and regional decline in speckle tracking analysis. The regional changes complied with RT fields.

Radiotherapy (RT) is an integral part of the treatment in half of cancer patients (1). Over 80% of early-stage breast cancer

patients receive adjuvant RT, which reduces the local recurrence risk by half and, the late breast cancer-related mortality by a fifth. The overall survival of early-stage breast cancer patients at 5 years is 91% in Finland (www.cancerregistry.fi). However, RT induces adverse effects in healthy tissue, which may lead to late dysfunction in adjacent organs. The heart is an important organ at risk, especially in left-sided breast cancer (LSBC). Breast cancer RT increases cardiac mortality and morbidity almost two-fold in long-term cohorts collected from patients treated with older RT techniques (2, 3). The modern RT treatment protocols have reduced cardiac radiation exposure. However, the clinical impact of the reduced cardiac dose will not be revealed until long-term data are available. In the meantime, early and mid-term cardiac changes are valuable in predicting later sequelae and to reveal the mechanism and time-course of RT-induced heart disease (RIDH).

RIHD can manifest as coronary artery disease, valvular lesions, heart failure, pericardial changes or conduction abnormalities. These changes occur usually several years or decades after RT treatment (2-4). The early subclinical RT-induced cardiac changes precede the late manifestations. Perfusion defects and changes in strain and strain rate corresponding to the RT fields have been detected 0-6 months after RT with myocardial perfusion imaging and with echocardiography (5-7). After chemotherapy, an early change in global longitudinal strain (GLS) predicts later decline in left ventricular ejection fraction (LVEF), but the knowledge of post-RT strain evolution is sparse (8, 9). The aim of our study was to explore the evolution of early RT-induced changes in speckle tracking echocardiography (STE) in early-stage breast cancer patients within the first three years after RT.

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Key Words: Breast cancer, radiotherapy, speckle tracking echocardiography, midterm follow-up.

Table I. Characteristics of the study group.

	Patients with right-sided breast cancer n=20		Patients with left-sided breast cancer n=61		p-Value
	Md	[Q ₁ , Q ₃]	Md	[Q ₁ , Q ₃]	
Age (years)	64	[60, 66]	64	[58, 67]	0.789
BMI (kg/m ²)	26.7	[24.7, 30.0]	26.3	[24.1, 29.9]	0.567
	n	%	n	%	
Concurrent diagnosis					
Hypertension	13	65.0	22	36.7	0.038
Diabetes	3	15.0	4	6.7	0.358
High cholesterol	4	20.0	14	23.3	1.000
Hypothyreosis	4	20.0	12	20.0	0.705
No concurrent other diagnosis	5	25.0	28	46.7	0.118
Smoking					
Current	2	10.0	9	15.0	0.722
Ever	4	20.0	16	26.7	0.767
Baseline medication					
Beta blockers	5	25.0	7	11.7	0.163
Calcium channel blockers	4	20.0	4	6.7	0.102
ACE/ARB	10	50.0	15	25.0	0.052
Statins	4	20.0	12	20.0	1.000
Cancer treatment					
Surgery					
Breast cancer resection	19	95.0	59	98.3	0.440
Breast cancer ablation	1	5.0	1	1.7	0.440
Hormonal therapy					
Use of AI	8	40.0	22	36.7	0.796
Use of tamoxifen	9	45.0	2	3.3	0.032
	Md	[Q ₁ , Q ₃]	Md	[Q ₁ , Q ₃]	
Radiotherapy					
Mean heart dose (Gy)	0.6	[0.4, 0.7]	3.1	[1.8, 4.0]	<0.001

BMI: Body mass index; ACE/ARB: angiotensin converting enzyme inhibitors or angiotensin receptor blockers; AI: aromatase inhibitor; Gy: Gray. Significant *p*-values (*p*<0.05) are shown in bold.

Patients and Methods

Patient selection. We included 81 eligible female patients with early-stage breast cancer into this single-center prospective study from July 2011 to November 2016. Sixty-one patients had left-sided (LSBC) and 20 patients had right-sided breast cancer (RSBC). All of the patients received adjuvant conformal three-dimensional (3D) RT after breast cancer surgery. The exclusion criteria have been described previously (7). Due to the early stage of the disease, no patient received chemotherapy. The study complied with the Helsinki Declaration, and the local institutional board of ethics approved the protocol (ETL R10160). All participants signed an informed consent before their enrollment.

Radiotherapy. RT was delivered according to normal institutional clinical guidelines either with 50 Gray (Gy) with 2 Gy fractions or 42.56 Gy with 2.66 Gy fractions as described in detail earlier (7).

Cardiac examinations. The patients were examined 6±8 days prior to RT, within three days after the end of RT and again three years post-RT (range=2.5-3.3 years). All echocardiographic examinations were performed by the same cardiologist (SST) using a Philips iE33 ultrasound machine (Bothell, WA, USA) and with 1-5 MHz matrix-array X5-1 transducer according to a predefined protocol (7). All off-line analysis was performed with the same Philips Qlab 10.1 version (Philips Qlab, Bothell, WA, USA). The analysis of variability for intraobserver and interobserver tests as well as for test-retest for the global, regional and segmental strain analysis have been previously reported (7).

Statistics. The data are presented as the means with standard deviations (SD) for variables with normal distribution and as medians with quartiles for non-normally distributed variables or as numbers with percentages. The difference between groups was tested with independent samples *t*-test, Mann Whitney *U*-test and Chi square or

Table II. Changes in global and regional strain in speckle tracking analysis in patients with left-sided breast cancer.

	Baseline n=54		After RT n=58		3 years control n=60		<i>p</i> -Value ¹	<i>p</i> -Value ²	<i>p</i> -Value ³
	Mean	SD	Mean	SD	Mean	SD			
Longitudinal strain									
Global	−18.4	3.1	−17.3	3.2	−16.8	3.1	0.003	0.001	0.146
Basal	−21.6	5.0	−23.2	4.9	−24.1	6.2	0.024	0.003	0.246
Mid	−19.4	4.6	−17.9	5.7	−17.8	5.8	0.039	0.022	0.845
Apical	−18.6	5.1	−16.8	4.8	−15.4	4.5	0.003	<0.001	0.028
Anterior	−18.3	4.3	−17.7	4.5	−17.8	3.4	0.277	0.375	0.967
Anteroseptal	−19.1	4.0	−18.5	4.5	−16.9	4.8	0.281	0.040	0.015
Inferoseptal	−21.2	3.7	−20.2	3.9	−19.9	4.7	0.110	0.137	0.787
Inferior	−20.4	4.0	−19.6	4.9	−18.5	4.8	0.264	0.037	0.253
Inferolateral	−20.0	4.8	−19.0	4.8	−20.0	4.3	0.122	0.732	0.090
Anterolateral	−20.5	3.5	−20.4	4.4	−20.9	3.8	0.874	0.979	0.587
Circumferential strain									
Global	−30.1	4.7	−29.1	5.2	−29.7	5.2	0.072	0.158	0.593
Basal	−23.6	4.9	−22.8	5.3	−24.8	5.6	0.076	0.206	0.007
Mid	−30.3	6.2	−30.2	6.0	−30.7	5.7	0.525	0.646	0.845
Apical	−36.8	8.6	−35.3	8.0	−34.5	8.7	0.093	0.082	0.539
Anterior	−38.8	9.8	−38.3	9.6	−43.2	7.7	0.216	0.008	<0.001
Anteroseptal	−33.1	6.8	−31.3	7.6	−29.2	6.3	0.085	<0.001	0.048
Inferoseptal	−30.5	7.1	−29.9	6.3	−31.5	6.2	0.400	0.497	0.047
Inferior	−31.6	6.2	−32.3	7.5	−34.3	7.4	0.773	0.016	0.053
Inferolateral	−29.6	6.4	−28.6	6.3	−28.8	5.9	0.122	0.732	0.090
Anterolateral	−26.5	6.6	−26.1	6.3	−26.4	6.0	0.754	0.580	0.579

RT: Radiotherapy. *p*-Value¹, *p*-Value² and *p*-Value³ present statistical significance of the changes in strain values between baseline and after RT, between baseline and at the 3 year follow-up examination and between values measured after RT and at the 3 year follow-up examination, respectively. Significant *p*-values (*p*<0.05) are shown in bold.

Fisher's test for variables with normal and non-normal distribution and for categorical variables, respectively. The changes of the variables were tested with paired samples *t*-test, Wilcoxon signed rank test and related-samples McNemar's test when appropriate. Univariate and multivariable analysis was performed with linear (numerical data) or logistic regression model. Multivariable analysis was performed with forward stepwise analysis for age, hypertension, smoking history, the use of an angiotensin converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB), the use of a statin, the use of an aromatase inhibitor (AI) and for mean heart radiation dose. The analysis was performed with IBM SPSS version 24.

Results

General characteristics. The characteristics of the population are shown in Table I. The mean age of the patients at inclusion was 64 years (range=49-83 years). Thirty-three patients (41%) had no other concurrent diagnosis, 60 (74%) patients were non-smokers and 29 (38%) patients had normal body mass index (BMI under 25 kg/m²). The most prevalent concurrent diseases were hypertension (35 patients, 45%) and dyslipidemia (19 patients, 24%).

Regional analysis of the longitudinal strain. At three-year follow-up, the changes from baseline in the regional and

segmental longitudinal strains were more prevalent in the patients with LSBC than in those with RSBC (Tables II and III, Figure 1). In patients with LSBC, the number of segments with a significant reduction increased from five segments immediately after RT to 7 segments at three-year follow-up, and were located in the apical and anteroseptal regions (Figure 1). Furthermore, there was a significant worsening of the longitudinal strain between post-RT and the three-year follow-up examination in the apical and anteroseptal regions, while the changes were maintained in the mid and inferior regions without significant change from post-RT to the three-year follow-up examination (Table II). The basal area of the left ventricle (LV) displayed increased function in both segmental and regional levels. Patients with RSBC had RT-induced reduction in the basal anterior segments throughout the follow-up period.

In the whole study population, the strain in the apical region (including the six apical segments and the apex) was $-17.9 \pm 5.3\%$ at baseline, $-17.0 \pm 4.7\%$ post-RT (*p*<0.001 baseline vs. post-RT) and $-15.8 \pm 4.5\%$ at the three-year follow-up (*p*=0.002 baseline vs. three-year follow-up and *p*=0.024 post-RT vs. three-year control). There was a difference between patients with LSBC and RSBC. In patients with LSBC, the apical strain declined by $3.2 \pm 5.5\%$ (*p*<0.001) while in patients

Table III. Changes in global and regional strain in speckle tracking analysis in patients with right-sided breast cancer.

	Baseline n=20		After RT n=20		3 years control examination n=20				
	Mean	SD	Mean	SD	Mean	SD	<i>p</i> -Value ¹	<i>p</i> -Value ²	<i>p</i> -Value ³
Longitudinal strain									
Global	−16.9	3.8	−17.2	2.8	−17.7	2.9	0.577	0.489	0.626
Basal	−21.1	4.3	−20.3	4.2	−20.7	3.5	0.567	0.755	0.620
Mid	−17.6	5.3	−18.5	5.0	−19.3	5.0	0.489	0.275	0.468
Apical	−16.3	5.6	−17.7	4.1	−17.0	4.6	0.197	0.547	0.510
Anterior	−18.4	4.3	−16.7	4.8	−17.0	4.2	0.089	0.155	0.624
Anteroseptal	−16.6	4.6	−18.2	5.2	−17.5	4.1	0.374	0.370	0.645
Inferoseptal	−19.1	3.8	−20.2	4.0	−20.6	4.7	0.229	0.216	0.663
Inferior	−19.8	4.7	−19.4	2.9	−19.6	4.8	0.854	0.645	0.933
Inferolateral	−18.6	4.3	−19.0	3.4	−20.6	4.6	0.704	0.093	0.473
Anterolateral	−19.3	5.0	−20.0	3.5	−20.1	3.7	0.528	0.479	0.889
Circumferential strain									
Global	−29.6	7.2	−27.9	5.1	−30.4	6.9	0.218	0.813	0.151
Basal	−23.8	6.8	−21.2	5.2	−24.5	7.6	0.118	0.971	0.157
Mid	−29.0	8.3	−29.4	6.0	−31.4	6.3	0.811	0.269	0.199
Apical	−36.6	13.0	−36.8	11.3	−36.4	11.0	0.353	0.926	0.958
Anterior	−35.1	9.5	−34.3	8.5	−42.5	10.3	0.455	0.021	0.008
Anteroseptal	−34.1	10.5	−34.0	7.8	−31.0	6.9	0.863	0.112	0.154
Inferoseptal	−31.0	7.9	−28.9	7.6	−30.7	6.2	0.169	0.826	0.165
Inferior	−30.7	8.5	−28.2	8.1	−36.0	6.3	0.279	0.006	0.002
Inferolateral	−29.1	7.9	−30.1	8.0	−29.0	9.0	0.704	0.093	0.473
Anterolateral	−27.5	7.9	−25.6	6.6	−28.7	7.9	0.146	0.592	0.239

RT: Radiotherapy. The *p*-Value¹, *p*-Value² and *p*-Value³ values present the statistical significance of the changes in strain values between baseline and after RT value, baseline and 3 year follow-up examination values and between values measured after RT and at the 3 year follow-up examination, respectively. Significant *p*-values (*p*<0.05) are shown in bold.

with RSBC, the apical strain increased by $0.7 \pm 5.2\%$ ($p=0.547$) at the three-year follow-up compared to the baseline (LSBC vs. RSBC change $p=0.007$). In multivariable analysis, AI use had an independent association with the apical strain change at three-year follow-up in patients with LSBC ($\beta=-4.494$, $p=0.004$). In patients with RSBC, AI use ($\beta=-6.409$, $p<0.001$), mean heart radiation dose ($\beta=2.496$, $p=0.002$) and ACE/ARB use ($\beta=-3.881$, $p=0.017$) had independent associations with the apical strain change at the three-year follow-up. The influence of AI use on apical strain is illustrated in Figure 2. Patients with RSBC using AI had an apical strain decline of $3.6 \pm 5.2\%$ while patients not using AI had an increase in apical strain by $3.6 \pm 2.8\%$ ($p<0.001$). In the whole study population, patients using AI had a reduction of $3.0 \pm 3.9\%$ ($p=0.001$) and $5.4 \pm 5.9\%$ ($p<0.001$), while patients not using AI showed an initial increase of $0.1 \pm 4.8\%$ ($p=0.858$) and a later decline of $0.3 \pm 4.8\%$ ($p=0.696$) after RT and at the three-year follow-up examination, respectively.

Global longitudinal strain. GLS was $-18.0 \pm 3.3\%$ at the baseline. It declined to $-17.2 \pm 3.1\%$ ($p=0.028$) immediately after RT and to $-17.0 \pm 3.0\%$ ($p=0.015$) at the three-year follow-up examination in the whole group. At the post-RT and at the

three-year follow-up examinations, GLS was over 15% lower than at the baseline (GLS15) in fourteen (19%) and 19 patients (27%), respectively. The GLS decline was higher in patients with LSBC vs. RSBC after RT ($1.1 \pm 2.7\%$ decline vs. $0.4 \pm 2.6\%$ increase, $p=0.040$) and at the three-year follow-up ($1.7 \pm 2.8\%$ decline vs. $0.0 \pm 4.4\%$ change, $p=0.102$). GLS15 rates were not different in patients with LSBC and RSBC patients after RT (12 vs. 2 patients, $p=0.324$) and at the three-year follow-up (15 vs. 4 patients, $p=0.763$). In multivariable analysis, AI use ($\beta=-1.977$, $p=0.001$) was independently associated with GLS15. Patients using AI had GLS decline by $2.0 \pm 2.4\%$ (vs. $0.0 \pm 2.7\%$ in patients not using AI, $p=0.001$) after RT and by $3.2 \pm 4.2\%$ (vs. $0.2 \pm 3.2\%$ decline in patients not using AI, $p=0.001$) at the three-year follow-up examination. Post-RT GLS15 was observed in 10 patients (14%) using AI and in 4 patients (6%) not using AI ($p=0.005$). At the three-year follow-up examination, 13 AI users (18%) and 6 (9%) of the non-users ($p=0.001$) had a GLS15.

Circumferential strain and rotation of the left ventricle. Post-RT, there were no significant changes in the circumferential strain neither in patients with LSBC nor in those with RSBC. However, at the three-year follow-up examination, regional

Figure 1. Segmental changes of the left ventricle in longitudinal strain after radiotherapy (figures on the left) and at the three-year follow-up (figures on the right). The red color shows segments with worsening function and green those with better function. The darker colors show segments with statistically significant changes ($p < 0.05$). Patients with left-sided breast cancer are shown on the top row and patients with right-sided breast cancer on the bottom row.

changes were observed in both groups. In patients with LSBC, basal, anterior, inferoseptal and inferior regions presented increased function, while anteroseptal regions presented declined function (Table II). Patients with RSBC had an increase in the anterior and inferior segments (Table III).

The changes in rotation of the LV are shown in Table IV. Patients with LSBC had no significant changes in LV rotation, while patients with RSBC had a significant decline in basal rotation, as well as delayed rotation both in the basal and apical segments.

Conventional echocardiography. The results of the conventional echocardiography measurements are displayed

in Table V. The changes were more prevalent in patients with LSBC both after RT and at the three-year follow-up examination.

Discussion

This study demonstrated that the initial RT-induced changes not only persisted, but they were also aggravated at three-year follow-up. Patients with LSBC had an apical and anteroseptal deterioration that was exaggerated at the three-year follow-up examination, while the three-year changes were most prominent in circumferential function and in the rotation of LV in patients with RSBC.

Figure 2. Changes in apical strain in the follow-up according to breast cancer laterality and the use of aromatase inhibitors. Patients with left-sided breast cancer are shown on the left side (A) and patients with right-sided breast cancer on the right side (B). The box plots are colored with blue, green and yellow for baseline, post-radiotherapy and three-year follow-up studies, respectively. Patients not using aromatase inhibitors display a marginal strain decline in patients with left-sided breast cancer, while patients with right-sided breast cancer display an increasing function. Patients using aromatase inhibitors have a significant apical functional decline in both groups.

Table IV. Changes in the left ventricular rotation after breast cancer radiotherapy.

	Baseline		After RT		3 years control		<i>p</i> -Value ¹	<i>p</i> -Value ²	<i>p</i> -Value ³
	Md	[Q1, Q3]	Md	[Q1, Q3]	Md	[Q1, Q3]			
Left-sided breast cancer (n=61)									
Basal rotation (°)	−10.5	[−13.0, −7.6]	−10.1	[−13.2, −7.1]	−8.8	[−13.0, −6.5]	0.862	0.313	0.462
Time BR (ms)	344	[288, 426]	383	[311, 443]	364	[297, 459]	0.294	0.660	0.806
Apical rotation (°)	5.8	[3.8, 10.9]	8.0	[4.4, 10.9]	7.4	[4.0, 11.2]	0.356	0.739	0.436
Time AR (ms)	379	[289, 455]	392	[313, 469]	357	[315, 462]	0.735	0.861	0.889
Twist (°)	16.2	[12.6, 19.0]	16.5	[12.3, 23.7]	16.2	[11.2, 21.2]	0.285	0.524	0.296
Right-sided breast cancer (n=20)									
Basal rotation (°)	−9.5	[−12.6, −7.1]	−8.7	[−12.6, −4.2]	−7.8	[−9.7, −5.4]	0.295	0.030	0.212
Time BR (ms)	316	[246, 448]	331	[208, 450]	397	[296, 539]	0.809	0.070	0.011
Apical rotation (°)	10.1	[3.9, 16.0]	8.1	[4.0, 12.0]	8.7	[5.9, 15.2]	0.231	0.469	0.306
Time AR (ms)	334	[245, 469]	325	[260, 423]	401	[299, 483]	0.420	0.049	0.035
Twist (°)	18.0	[14.3, 25.4]	15.0	[12.5, 19.8]	16.5	[14.7, 23.4]	0.227	0.629	0.421

RT: Radiotherapy; Time BR and AR, time of peak basal and apical rotation adjusted to heart rate. Twist is calculated as the difference between maximal basal and apical rotations. The *p*-Value¹, *p*-Value² and *p*-Value³ present statistical significance of the changes in the strain values between baseline and after RT value, baseline and at the 3 year follow-up examination values and between values measured after RT and at the 3 year follow-up examination, respectively. Significant *p*-values (*p*<0.05) are shown in bold.

Radiotherapy-induced changes. Post-RT tissue changes have been well described in previous studies by Fajardo and Khan (10, 11). Ionization leads to inflammatory changes within minutes, which subsides within weeks after cessation of RT. Thereafter, endothelial damage leads to capillary rarefaction, and a fibrotic cascade is initiated (12).

Likewise, the initial cardiac changes are inflammatory followed by a latent phase (2). The early changes, though currently rare, include pericardial irritation with pericarditis and fluid accumulation. In the latent phase between the inflammatory period and late clinical fibrotic phase, signs of capillary rarefaction and initial myocardial fibrotic

Table V. Conventional echocardiography measurements at baseline, after radiotherapy and at 3 year follow-up examination.

	Baseline		After RT		3 years control		<i>p</i> -Value ¹	<i>p</i> -Value ²	<i>p</i> -Value ³
	Mean	SD	Mean	SD	Mean	SD			
Left-sided breast cancer (n=61)									
Structures									
LVEDD (mm)	45.1	4.1	44.7	3.9	45.2	4.4	0.157	0.904	0.316
LVEDS (mm)	30.3	3.4	30.0	3.6	30.2	3.5	0.462	0.717	0.735
LV mass (g)*	152	[134, 174]	165	[139, 186]	161	[129, 177]	0.017	0.487	0.009
RV basal (mm)	34.1	5.0	33.6	4.5	35.0	4.2	0.340	0.267	0.038
Systole									
LVEF (%)	65	7	65	7	59	7	0.810	<0.001	<0.001
TAPSE (mm)	24.2	3.9	22.3	4.0	23.3	4.3	<0.001	0.086	0.051
Diastole and filling pressures									
LAVI (ml/m ²)	33	8	32	8	35	9	0.432	0.036	<0.001
Mitral E (cm/s)	72	15	69	14	70	17	0.015	0.258	0.612
Mitral dt (ms)	234	42	242	47	246	62	0.132	0.175	0.638
Mitral ea-ratio*	0.95	[0.77, 1.06]	0.88	[0.75, 1.13]	0.87	[0.77, 1.13]	0.444	0.742	0.795
Mitral Ee'-ratio*	8.8	[7.2, 10.9]	8.5	[7.1, 10.0]	8.6	[7.1, 10.4]	0.183	0.310	0.242
Tr gr (mmHg)	21.5	5.6	21.4	4.7	23.5	6.0	0.677	0.011	0.012
IVC (mm)	15.7	3.6	14.6	3.4	15.3	4.1	0.024	0.474	0.183
vIVC (%)*	60	[52, 70]	62	[54, 73]	55	[41, 68]	0.132	0.013	0.001
Right-sided breast cancer (n=20)									
Structures									
LVEDD (mm)	43.8	4.6	43.8	3.9	44.1	4.7	0.896	0.544	0.679
LVEDS (mm)	29.7	3.2	29.3	3.4	30.5	3.2	0.428	0.098	0.093
LV mass (g)*	146	[125, 182]	158	[136, 208]	146	[123, 193]	0.017	0.970	0.067
RV basal (mm)	34.3	6.0	33.6	5.7	35.0	4.9	0.522	0.489	0.182
Systole									
LVEF (%)	64	10	66	6	59	7	0.616	0.048	<0.001
TAPSE (mm)	23.9	5.4	22.5	5.2	22.7	4.2	0.141	0.186	0.917
Diastole and filling pressures									
LAVI (ml/m ²)	30	9	31	7	32	10	0.784	0.178	0.174
Mitral E (cm/s)	78	19	72	18	71	18	0.041	0.033	0.671
Mitral dt (ms)	211	42	243	51	227	55	0.011	0.255	0.362
Mitral Ea-ratio*	1.02	[0.78, 1.23]	1.00	[0.69, 1.09]	0.87	[0.70, 1.08]	0.279	0.044	0.575
Mitral Ee'-ratio*	10.1	[7.6, 12.4]	9.3	[7.5, 11.7]	8.9	[7.7, 11.1]	0.970	0.940	0.823
Tr gr (mmHg)	23.0	6.9	20.6	6.1	24.9	7.6	0.025	0.125	0.031
IVC (mm)	16.5	3.8	16.3	3.0	16.2	4.1	0.767	0.777	0.949
vIVC (%)*	61	[43, 73]	52	[39, 61]	46	[41, 57]	0.145	0.021	0.411

LVEDD and LVEDS: Left ventricular end-diastolic and end-systolic diameters, respectively; LV: left ventricular; RV: right ventricular; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; LAVI: left atrial volume indexed to body surface area; Mitral E, dt, Ea and Ee': Mitral inflow early diastolic velocity, declaration time of the early inflow, the ratio between early inflow and late inflow velocities and the ratio between early mitral inflow velocity and averaged pulsed tissue Doppler early diastolic velocities derived from basal anterior, septal, posterior and lateral LV walls, respectively; IVC and cIVC: inferior vena cava maximal diameter and its variation, respectively. *marks parameters with non-normal distribution. They are presented as medians with [Q1, Q3]. The *p*-Value¹, *p*-Value² and *p*-Value³ present statistical significance of the differences in strain values between baseline and after RT value, baseline and at 3 year follow-up values and between values measured after RT and value at the 3 year follow examination, respectively. Significant *p*-values (*p*<0.05) are shown in bold.

changes are induced (12). They can be detected as perfusion defects (myocardial perfusion imaging) or as subclinical myocardial functional changes (echocardiography) (13, 14). Late emerging fibrotic sequelae lead to coronary obstruction, retraction and calcification of the heart valves, and pericardial and myocardial fibrosis leading to

constriction and diastolic dysfunction as well as conduction abnormalities (2, 3).

Global longitudinal strain. GLS is an early and sensitive marker of LV functional decline over a wide range of diseases (15-17). In cancer patients receiving chemotherapy, an early

GLS decline has been associated with later LVEF deterioration (8). A 15% change from the initial value is considered to be clinically significant (4). Changes in LV strain after RT have been described earlier, but their prognostic impact is unclear (8, 9). In our patients, the initial GLS change persisted in the three-year follow-up, which may implicate permanent damage. Even more important and worrying is our finding that the proportion of patients with GLS15 increased during the follow-up period. In addition, the mean LVEF was lower at the three-year follow-up than at the baseline. This decline, however, was clinically insignificant and falls into limits of LVEF general variability, but the finding is in concordance with the changes in GLS. The initial strain changes may have been related to the early inflammatory reaction, whereas persisting, and progressive changes at the three-year follow-up examination may indicate the presence of a more permanent fibrotic process.

Regional longitudinal and circumferential strain changes according to breast cancer side. Both patients with LSBC and RSBC displayed further evolution of the initial post-RT changes at the three-year follow-up examination but in a different way. The patients with LSBC had reductions of strain in the areas where RT fields affected the heart, mainly in the antero-apical regions. At the three-year follow-up, the longitudinal strain was even more influenced in these regions. In general, circumferential strain increased, possibly as a compensatory mechanism, except for the anteroapical regions at the three-year follow-up examination in patients with LSBC. This indicates that the impact of RT is more severe and progressive on the anteroapical parts of the heart.

The impact of RT on cardiac function was subtler in patients with RSBC. The longitudinal strain was affected only at the basal anterior segment. However, circumferential strain increased with a similar pattern as in patients with LSBC. Furthermore, basal rotation diminished and both apical and basal rotations were delayed. Changes in LV rotation have been observed at the early phase of many cardiac diseases, and they even precede changes in longitudinal and circumferential strain (18). Aging, hypertension, hypertrophic cardiomyopathy and aortic stenosis are all characterized by increased apical rotation and delayed rotation with longer untwisting (18-22). Anthracycline treatment has induced a decline in both apical and basal rotation along with an overall twist becoming declined and delayed (23). It can be hypothesized that patients with RSBC were affected by a similar process.

The role of AI versus RT. In multivariable analysis, AI use had an independent association with several strain changes. AI use inhibits the final pathway of estrogen metabolism, which has been shown to be detrimental to myocardial function and cardiovascular prognosis (24, 25). Whether this negative effect seen in our patients is a reversible or long-

lasting effect is not clear, while all thirty of our patients who were AI-users (37%) were still using AI at the three-year follow-up examination.

Even though the association of cardiac changes was even stronger with AI use than with RT, the effect is probably additive. The timing of initiation of AI treatment was not recorded, but according to clinical practice, at least some of our patients had started their AI treatment prior to RT, and hence, the changes from baseline to post-RT present an additive effect. Furthermore, the distribution of the regional changes presents the effect of RT, and cannot be explained by AI use only. Therefore, in a sense, AI use seems to be at least a sensitizer of the RT-induced effects. However, since the patients were still using AI at the three-year follow-up examination, it is unclear whether the effect of AI on myocardial function is transient or whether the concurrent use of AI during RT actually generates more severe myocardial damage. This issue will be addressed in the later follow-up of this patient group.

Clinical Implications

The most important clinical finding of our study is that even modern 3D breast cancer RT induced long-standing echocardiographic changes. Taking into account the progressive nature of these changes, it is possible that the patients have an elevated risk of RIHD. In our study, no patient developed symptomatic cardiac diseases during the three-year follow-up. This study population will be followed up further, and the coming years will reveal the later development of these changes and their clinical significance.

Limitations of our Study

The results of this study present three-year changes and their associations to later clinical events are still unclear. Furthermore, this study was neither designed nor powered to explore the influence of medications, and a specific study to explore the role of AI in this context is needed.

Conclusion

STE was able to detect the continuous decline in LV function at three-year follow-up. In patients with LSBC, longitudinal strain in global, regional and segmental levels declined, while patients with RSBC experienced circumferential strain increase and negative changes in rotation. AI use aggravated the changes in strain in both groups.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors have participated in the conception of this study and contributed to the article's content, critically revised the manuscript and approved the final version. TS and PLKL were responsible for recruiting the patients for this study and for calculations of cardiac radiation doses. ST acquired all echocardiographic data and analyzed them. The statistical analysis was performed by ST and HH.

Acknowledgements

The Authors thank the research nurses Virpi Palomäki, Hanna-Leena Näppilä, Kati Helleharju and Katri Mikkonen for their expert assistance during the study.

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Received May 12, 2019

Revised June 9, 2019

Accepted June 12, 2019