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Early Effects of Adjuvant Breast Cancer Radiotherapy on Right Ventricular Systolic and Diastolic Function

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Abstract. *Aim: Reduced right ventricular (RV) systolic function correlates with poor prognosis in several heart diseases. The aim of this prospective single-Center study was to investigate whether conformal three-dimensional (3D) breast cancer radiotherapy impairs RV function. Patients and Methods: Forty-nine patients with early-stage left-sided breast cancer underwent comprehensive two-dimensional (2D) echocardiography before and after radiotherapy. RV function was evaluated with tricuspid annular plane systolic excursion (TAPSE), pulsed tissue Doppler peak velocity at the lateral RV wall (S') and RV and venous flow analysis. Results: Radiotherapy reduced TAPSE from 24.5±4.0 mm to 22.4±3.9 mm (p<0.001), S' from 12.7±3.1 m/s to 12.2±2.7 m/s (p=0.11) and pulmonary flow velocity time integral (VTI) from 16.6±3.1 cm to 15.9±2.3 cm (p=0.07), respectively. These changes were unrelated to changes in LV function. Conclusion: Modern radiotherapy reduced RV systolic function. As a readily-available and sensitive measurement, TAPSE is as a practical tool for detection of radiotherapy-induced cardiac changes.*

Breast cancer is the most common cancer in women (1). Improved diagnostics and adjuvant therapies have increased breast cancer survival rates (2). On the other hand, cardiac exposure from adjuvant radiotherapy (RT) has been shown to cause adverse cardiovascular effects. The late sequel includes left ventricular (LV) dysfunction, valvular heart disease and coronary artery disease (3-6). It is important for cardiologists and oncologists to recognize these adverse effects and find means to limit late co-morbidities.

Several investigators have demonstrated that the reduction of right ventricular (RV) systolic performance correlates with poor prognosis across a broad spectrum of diseases (7-9). Despite the important prognostic role of RV function, no prior study has systematically evaluated the effects of breast cancer RT on RV function. The aim of this prospective single-Center study was to investigate whether modern conformal three-dimensional (3D) breast cancer RT impairs RV systolic and diastolic function in the early phase.

Patients and Methods

Patient selection. Forty-nine eligible female patients with an early left-sided breast cancer who received postoperative adjuvant conformal RT without concomitant chemotherapy were included in this single-Center, prospective study. The study was conducted from July 2011 to February 2013. The exclusion criteria were age under 18 years or over 80 years, other malignancy, pregnancy or breast feeding, acute myocardial infarction within 6 months, symptomatic heart failure (NYHA 3-4), dialysis, permanent anti-coagulation and severe psychiatric disorder. To optimize echocardiography image quality, patients with atrial fibrillation, left bundle branch block (LBBB), pacemaker therapy and severe lung disease were excluded. The institutional board of ethics approved the protocol and all participants signed informed consent before enrollment in the study.

Radiotherapy. All patients underwent 3D computer tomography (CT)-based treatment planning (Philips Big Bore CT; Philips Medical Systems, Madison, WI, USA) in a supine position on a

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Key Words: Radiotherapy, breast cancer, right ventricle, TAPSE.

Table I. *Radiation doses to the different cardiac structures (N=49)*[*]

	Mean±SD Gy[†]	Max±SD Gy[‡]
Whole heart	3.27±1.53	46.17±9.09
Left ventricle	5.41±3.03	44.44±9.52
LAD	20.35±10.63	41.87±13.15
Right ventricle	3.03±2.03	32.06±15.57
Free wall of right ventricle	6.09±4.74	31.91±15.62
Ipsilateral pulmonary dose	8.03±2.01	50.65±5.14

Gy, Grey; LAD, region of the heart perfused by left anterior descending coronary artery; SD, standard deviation. [*]The radiation doses are derived from three-dimensional (3D) computed tomography (CT) planning pictures by manual tracing. [†]The average dose to the appointed volume. [‡]The maximum point dose to the appointed volume.

Table II. *Baseline characteristics of the study cohort (N=49).*

Variable	Mean±SD
Age (years)	63±6
Systolic blood pressure (mmHg)[*]	145±19
Diastolic blood pressure (mmHg)	80±12
Height (cm)	164±6
Weight (kg)	73±13
Body mass index (kg/m^2)	27±4
Body surface area (m^2)	1.80±0.17
	N (%)
Smoking	
Previous	5 (10%)
Current	8 (16%)
Prior diagnosis[†]	
Hypertonia	17 (35%)
Diabetes mellitus	2 (4%)
Hypercholesterolemia	8 (16%)
Hypothyreosis	5 (10%)
Atherosclerosis	2 (4%)
Significant valvular abnormality	2 (4%)
Medical treatment	
Beta blocker	6 (12%)
Calcium channel blocker	2 (4%)
ACE inhibitors/ARBs	10 (20%)
Diuretics	5 (10%)
Thyroxin	5 (10%)
Nitrates	1 (2%)
Aspirin	3 (6%)
Statin	7 (14%)
Oral diabetes medication	2 (4%)

ACE, Angiotensin-converting enzyme; ARB, angiotensin II blocker. [*]Measured at first visit. [†]Defined as medication requiring disease state. The values are presented either as the mean±SD (standard deviation) or the number of cases and percentage in the present study population.

breast board with 3 mm thick slices. The breath-hold technique was not used. Treatment planning and contouring were performed with an Eclipse v.10 system (Varian Medical Systems, Palo Alto, CA, USA). Heart contouring was performed by the same oncologist (TS). Treatment doses were either 50 Gy in 2 Gy fractions (standard) or 42.56 Gy in 2.66 Gy fractions (hypofractionated) according to the local guidelines. An additional boost of 16 Gy in 2 Gy fractions to the tumor bed was used if clinically indicated. Doses were calculated using the anisotropic analytical algorithm (AAA) (Figure 1) and dose-volume histograms (DVHs) for different structures were generated for each patient (Table I). The average treatment time was 36±10 days (20-70 days).

Echocardiographic examinations. A comprehensive echocardiography and electrocardiography (ECG) were performed at baseline and at the end of RT (1.0±2.8 days from the last radiation dose). All examinations were performed with the same cardiac ultrasound machine (Philips iE33; Philips, Bothell, WA, USA) and a 1-5 MHz matrix-array X5-1 transducer by the same cardiologist (SST). The interval between the baseline and control studies was 41±11 days. All images were acquired at rest with a simultaneous superimposed ECG. Subcostal imaging was performed in a supine position and other imaging was performed with the patient in the left lateral decubitus position. Doppler recordings were acquired at the end expiration during shallow breathing. Raw data were stored digitally for offline analysis with the Qlab software (Philips). RV systolic performance was measured in an apical four chamber view. Care was taken to identify the true apex and optimize the depth and the sector width of the image. Tricuspid annular plane systolic excursion (TAPSE) was measured with the M-mode cursor placed between the junction of the tricuspid valve and the RV lateral free wall annulus as total displacement of the tricuspid annulus from end-diastole to end-systole. Pulsed tissue Doppler was acquired from a point 1-1.5 cm apical from lateral tricuspid annulus (Figure 2). A 12-lead ECG was recorded at each visit.

Statistical analysis. Means and standard deviations were given for normally-distributed variables and medians and ranges for continuous variables with skewed distributions. Differences between measurements were tested by the paired samples *t*-test or by the Wilcoxon signed-rank test. The Spearman correlation was used to test the linear associations between variables. The associations between TAPSE and other variables were analyzed by the independent samples Mann-Whitney U test (continuous variables) or by the Fisher's exact test (categorical variables). All tests were two-sided and p values <0.05 were considered statistically significant. Statistical analyses were performed using the IBM SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.) statistical software package (http://www-01.ibm.com/software/analytics/spss/).

Results

General characteristics. The baseline characteristics of the patients are presented in Table II. The mean age of the population was 63 (range=49–79) years. The most common underlying diseases included hypertension (35%), hypercholesterolemia (16%), hypothyreosis (10%) and diabetes (4%). Twenty-two percent of the patients had no other diseases.

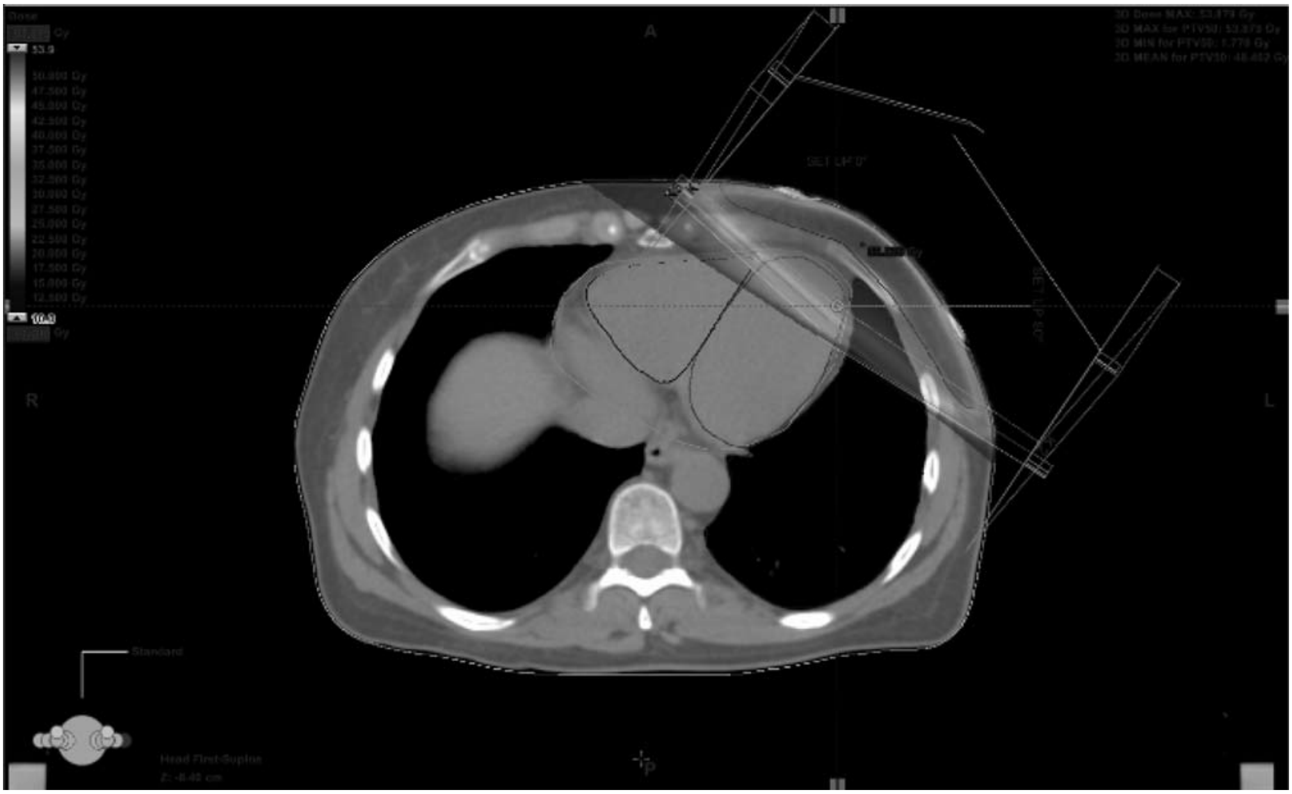

Figure 1. *Three-dimensional (3D) computed tomography (CT) treatment planning. Target volume is planned to cover remaining breast tissue. The dark area shows sites achieving more than 10 Grays with highest dose in the apex. Manually depicted heart contouring is also shown for the whole heart, left ventricle, right ventricle, right ventricle's free wall.*

RV echocardiographic measurements. RT caused significant changes in RV systolic function (Table III). TAPSE declined in 67% of the patients. The average reduction was 2.1±3.2 mm (p<0.001). A decrease of 4 mm or more was observed in 39% of the patients. There was no correlation between these changes and the cardiac or pulmonary radiation dose, smoking, ECG changes, body mass index (BMI) or underlying disease, other than hypothyreosis. The use of thyroxin (p=0.03) and diuretics (p=0.03) were associated with smaller TAPSE reduction. Likewise, the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) tended to protect against TAPSE decline (p=0.06). The reduction in TAPSE was 1.0±4.0 mm and 2.4±3.0 mm (p=0.22) among patients using and not using ACEIs/ARBs, respectively.

In keeping with the reduction of TAPSE, the other RV systolic parameters showed a declining tendency, although statistical significance was not reached. S' declined from 12.7±3.1 to 12.2±2.7 (p=0.11) and pulmonary flow VTI decreased from 16.6±3.1 to 15.9±2.3 (p=0.07). Isovolumetric velocity (IVV) (p=0.82) and acceleration of the IVV did not change (p=0.43) (Table III). Neither TAPSE nor any other RV systolic parameter was related to LV systolic or diastolic changes.

The changes in the RV diastolic parameters were less obvious than the systolic parameters. The maximal diameter of the inferior *vena cava* was 15.7±4.1 mm at baseline and 14.8±3.5 mm after RT (p=0.12). Its respiratory variability remained unchanged. There were no significant changes in the tricuspid Ea and Ee' ratio, whereas the tricuspid inflow E wave showed a slight (48.5±8.5 cm/s *vs*. 45.6±8.4 cm/s) but not statistically significant reduction (p=0.10) (Table III).

Minor tricuspid and pulmonary regurgitation were observed in 94% and 69% of the patients, respectively. The regurgitation was hemodynamically insignificant in all patients and no patient had stenosis in the right-sided heart valves. There were no changes in tricuspid or pulmonary valve status between baseline and control examinations.

LV echocardiographic measurements. At baseline, LV dimensions and function were compatible with patient´s age and underlying disease profile in all participants. RT had no significant effect on LV systolic or diastolic function. However, both the interventricular septum (10.0±1.2 mm *vs*. 10.3±1.3 mm, p=0.02) and the posterior wall (9.7±1.0 mm *vs*. 10.3±1.2 mm, p=0.01) were slightly thicker after RT than at baseline (Table IV).

Table III. *Echocardiographic measurements of the right ventricle (N=49).*

	Baseline		Measurement after radiotherapy		*p*-Value
	Mean±SD	Median (range)	Mean±SD	Median (range)	
RV basal dimension (mm)	33.7±5.5	33.0 (24.0-44.0)	33.3±4.5	33.1 (22.1-44.4)	0.513
TAPSE (mm)	24.5±4.0	24 (16-33)	22.4±3.9	22 (16-33)	<0.001
S' (cm/s)	12.7±3.1	12.1 (8.9-22.2)	12.2±2.7	11.5 (8.9-20.7)	0.114
IVV (cm/s)	13.0±4.8	12.4 (4.9-29.3)	12.6±3.8	12.4 (4.6-21.9)	0.828
IVA (cm/s^2)	2.8±1.0	2.7 (1.0-5.1)	2.7±0.9	2.6 (1.3-5.1)	0.439
Pulmonary peak flow velocity (cm/s)	69.6±14.3	71.0 (46-101)	67.6±11.5	67.4 (47-92)	0.382
Pulmonary flow at (ms)	149.4±33.0	145 (71-239)	147.4±29.3	146 (85-204)	0.668
Pulmonary flow VTI (cm)	16.6±3.1	16.6 (10.9-24.4)	15.9±2.3	15.8 (11.5-22.4)	0.071
Tricuspid gradient (mmHg)*	21.6±5.8	22 (8-34; n=42)	21.2±5.0	22 (8-32; n=39)	0.430
Tricuspid inflow E velocity (cm/s)	48.5±8.7	48.3 (32.6-66.6)	45.6±8.4	45.2 (24.9-68.9)	0.096
Tricuspid inflow a velocity (cm/s)	38.3±8.0	37 (22.7-61.7)	37.5±8.0	37.6 (22.8-61.7)	0.547
Tricuspid inflow dt (ms)	236±73	235 (132-444)	257.5±65,8	252 (140-454)	0.212
Tricuspid Ea ratio	1.30±0.24	1.26 (0.88-1.85)	1.24±0.23	1.26 (0.75-1.81)	0.281
Tricuspid Ee' ratio	4.2±1.1	4.1 (2.5-7.3)	4.3±1.4	4.1 (2.1-8.0)	0.406
IVC maximal diameter (mm)	15.7±4.1	15.9 (1.6-25.9)	14.8±3.5	14.8 (8.8-22.5)	0.119
IVC respiration variability (%)†	62.8±15.2	60.2 (30.6-97.7)	63.8±15.5	62.8 (28.2-92.2)	0.670
Hepatic vein flow SD ratio‡	1.53±0.46	1.55 (0.9-2.8; n=36)	1.62±0.46	1.50 (0.7-3.9; n=35)	0.318

RV, Right ventricle; TAPSE, tricuspid annular plane systolic excursion; S' and IVV, systolic and isovolumetric velocity of pulsed tissue Doppler derived from the lateral basal RV free wall; IVA, acceleration of the IVV; at, acceleration time; VTI, velocity time integral; dt, declaration time; Ee' ratio, ratio between tricuspid inflow E-velocity and pulsed Doppler e' velocity derived from the RV basal free wall; IVC, inferior vena cava; Mean±SD, mean±standard deviation. *Measurable in 83%. †Inferior vena cava respiration variability tested with sniffing. ‡Hepatic vena flow SD ratio calculated as the ratio between the maximal velocities of systolic and diastolic components.

Six patients had moderate valvular abnormalities at the baseline echocardiography examination. Two of them had been diagnosed before (one with stenosis in aortic bioprosthesis and one with moderate mitral regurgitation) and 4 had a new diagnosis (one with moderate aortic stenosis, two with moderate mitral regurgitation and one with mild aortic regurgitation). There were no changes in aortic or mitral valve status between the baseline and control examinations.

ECG. Patients had sinus rhythm, narrow QRS complex and normal PQ and QT time in all ECG recordings. There were no signs of right atrial or ventricular abnormalities in any recordings. RT caused moderate T-wave alterations in 16 patients (33%). These changes did not correlate to the change in TAPSE.

Discussion

We demonstrated that RV systolic function was reduced in the early phase after modern conformal 3D left-sided breast cancer RT, despite a lack of changes in LV function. This novel finding indicates that measurement of RV function is a sensitive indicator of radiation-induced myocardial injury and an attractive tool for the follow-up of patients after RT.

RV function after RT. RV wall is thinner than the LV wall. Therefore, tissue swelling, reduced contractility and diastolic changes can be detected earlier in the RV than in the LV. In the current study, RT did not cause any significant changes in LV systolic or diastolic function, whereas the average decline in TAPSE was 2.1±3.2 mm and declined by 4 mm or more in 39% of the patients. The same tendency was found in the other RV systolic parameters. The changes in RV function were not accompanied by any significant changes in echocardiographic measures of pulmonary function and resistance. Moreover, there was no correlation between TAPSE decline and pulmonary radiation dose.

TAPSE and S' are measurements of RV longitudinal function, whereas IVV and VTI reflect rotational contractility and global RV function, respectively. Longitudinal contractility is the main determinant of RV systolic function (10, 11). The basal circumferential muscle fibers shared by the right and left ventricles initiate systolic contraction and cause rotational contraction (12). In elderly subjects and in diseases that overload the RV, the rotational contractility increases proportionally as the longitudinal contractility is reduced (14) and rotational contractility is increased (12-15). In our patients, the reductions in TAPSE, S' and pulmonary VTI were not accompanied by a compensatory increase in IVV. This indicates that TAPSE-alone may underestimate the RT-induced RV damage.

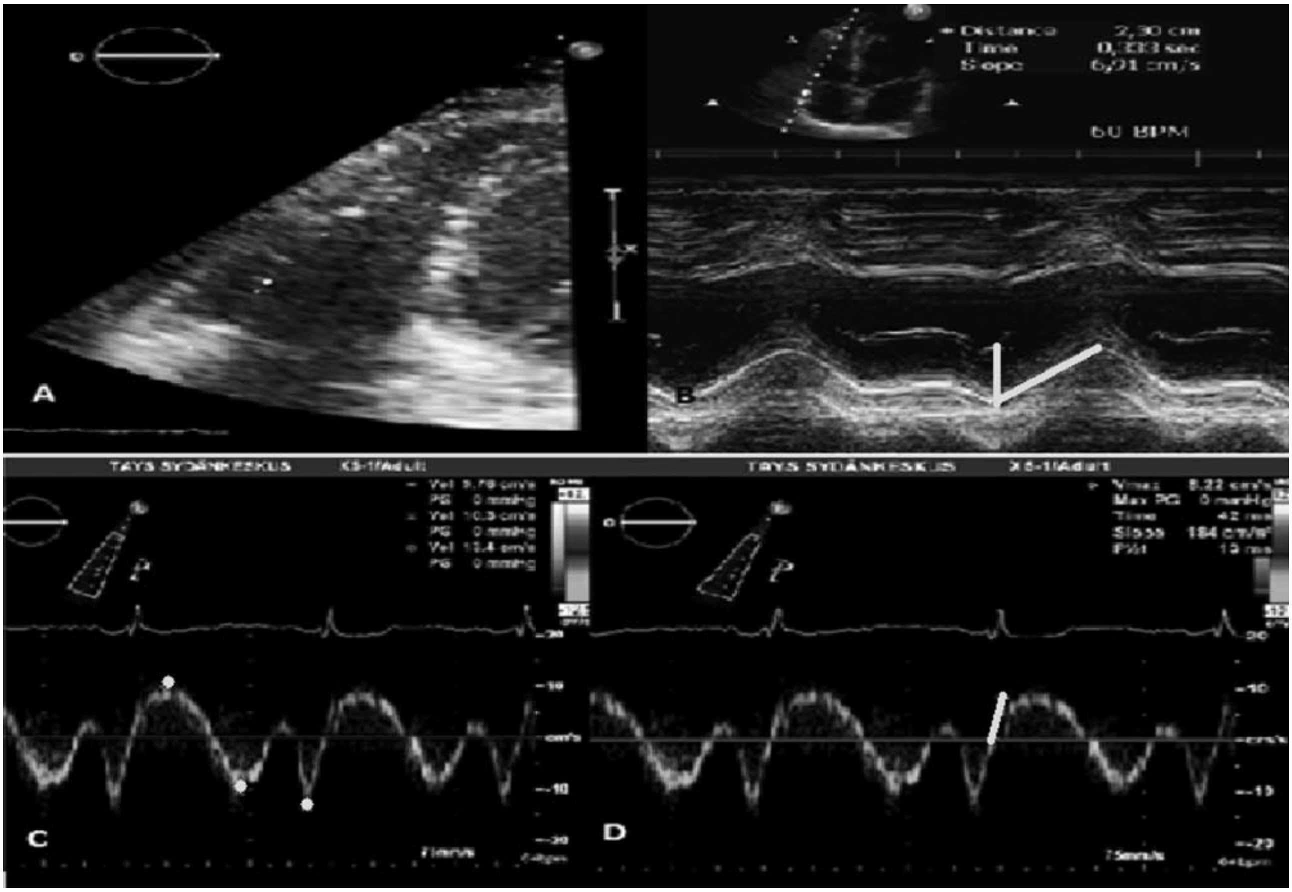

Figure 2. *Measurements of tricuspid annular plane systolic excursion (TAPSE) and pulsed tissue Doppler velocities at the lateral RV wall. A: Focused RV image with cursor placed in the junction of RV lateral wall and tricuspid annulus. B: TAPSE measurement with M-mode. C: Measurements of peak systolic velocity (S'), peak E' velocity and peak A' velocity, respectively. D: Measurements of IVV and IVA.*

Mechanism of the changes in RV function. The inflammatory reaction due to RT begins within hours (16, 17). The second or latent stage of radiation injury is characterized by reduced capillary density (17, 18). The complex fibrotic cascade is initiated as early as 2 weeks after the onset of RT (17, 19) and the earliest evidence of increased myocardial fibrosis has been observed within 40 days after a single radiation dose (16). Since our patients were exposed to RT for 4-5 weeks, all these mechanisms may contribute to the observed changes. Whether thyroxin or ACEI/ATR medication protects the RV from radiation-induced adverse effects remains to be established in larger clinical studies.

Limitations. Our study population was uniform in many ways, which reduced the confounding effects but also made extrapolation of the results to other groups difficult. Due to the small number of patients, a reliable multivariate analysis of related factors was not possible. Time-consuming magnetic resonance imaging and sophisticated 3D echocardiographic measurements were not used because the main idea was to determine whether the change in RV function could be measured with the tools we use in everyday practice.

Clinical implications of RV functional changes. The most important implication of this study was that the modern 3D conformal RT caused prominent changes in RV function in most of our patients. On the basis of the results of previous studies (3, 4), these changes may progress over time and clinically significant cardiac adverse events may emerge during long-term follow-up. These findings support the consensus statement recommending a comprehensive cardiac evaluation and a long-term follow-up of patients after breast cancer RT (20). According to our data, TAPSE is a more sensitive tool for the detection of the radiation-induced early myocardial deterioration than conventional LV measurements.

The result of this and prior studies imply that even small radiation doses may induce myocardial changes (21). In the

Table IV. *Echocardiographic measurements of the left ventricle*.

	Baseline		Measurement after radiotherapy		*p*-Value
	Mean±SD	Median (Range)	Mean±SD	Median (Range)	
LVEDD (mm)	45.4±4.1	45 (34.8-57.1)	44.7±4.1	45.2 (35.0-53.1)	0.084
LVESD (mm)	30.3±3.4	30.6 (18.9-40.0)	30.1±3.8	30.7 (19.0-36.7)	0.983
IVS (mm)	10.0±1.2	10.0 (8.0-12.8)	10.3±1.3	10.0 (8.0-13.0)	0.020
PW (mm)	9.7±1.0	10.0 (7.3-11.3)	10.3±1.2	10.0 (7.3-13.0)	0.011
LVEF (%)	62.2±5.0	62 (52-78)	61.5±5.2	62 (52-73)	0.473
Mitral inflow E (cm/s)	70±12	70 (47-102)	68±13	66 (39-109)	0.138
Mitral inflow a (cm/s)	77±19	74 (38-121)	75±14	77 (46-109)	0.128
Mitral inflow Ea-ratio	0.95±0.26	0.93 (0.56-1.78)	0.94±0.26	0.86 (0.59-1.67)	0.792
IVRT	104±26	103 (58-187)	109±21	106 (77-155)	0.283
Ee' ratio	9.0±2.6	8.7 (5.7-16.7)	8.8±2.1	8.5 (5.7-16.6)	0.554
LAVI (ml/m^2)	32.2±8.8	32.2 (16.7-56.3)	31.9±8.8	31.1 (13.7-53.2)	0.622
Pulmonary vein flow SD ratio	1.3±0.2	1.3 (0.8-1.8)	1.3±0.2	1.3 (0.7-1.8)	0.699

LVEDD, Left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; IVS, interventricular septum; PW, posterior wall; LVEF, left ventricular ejection fraction; IVRT, isovolumetric relaxation time; Ee' ratio, ratio between mitral inflow E-velocity, and averaged pulsed Doppler e' velocity derived from septal, lateral, anterior and inferior walls; LAVI, left atrial volume indexed to the patient's body surface area; Pulmonary vein flow SD ratio, ratio between systolic and diastolic peak velocities; Mean±SD, mean±standard deviation.

present study, the RV systolic function was impaired, although the mean dose to the RV free wall in our study group was only 6.09±4.74 Gy. Hence, it is important to use techniques that reduce cardiac radiation exposure, *e.g.* respiratory gating and breath-hold techniques.

Conclusion

Right ventricular systolic function is impaired after breast cancer adjuvant RT. TAPSE is a sensitive and reliable marker of early myocardial injury and can be used as a practical tool to identify patients who would benefit the most from a longterm follow-up.

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