A Higher Mean Heart Radiation Dose Induces Higher Frequency of Multiple Cardiac Changes

Tuohinen, Suvi Sirkku

2022-05

Tuohinen , S S , Aula , H , Skyttä , T , Huhtala , H , Keski-Pukkila , K , Nikus , K , Virtanen , V , Kellokumpu-Lehtinen , P-L & Raatikainen , P 2022 , ' A Higher Mean Heart Radiation Dose Induces Higher Frequency of Multiple Cardiac Changes ' , Anticancer Research , vol. 42 , no. 5 , pp. 2519-2529 . https://doi.org/10.21873/anticanres.15730

http://hdl.handle.net/10138/344349
https://doi.org/10.21873/anticanres.15730

ANTICANCER RESEARCH *42*: 2519-2529 (2022)
doi:10.21873/anticanres.15730

A Higher Mean Heart Radiation Dose Induces Higher Frequency of Multiple Cardiac Changes

SUVI SIRKKU TUOHINEN[1,2], HANNA AULA[3,4], TANJA SKYTTÄ[3,4], HEINI HUHTALA[5], KONSTA KESKI-PUKKILA[6], KJELL NIKUS[2,4], VESA VIRTANEN[2,4], PIRKKO-LIISA KELLOKUMPU-LEHTINEN[3,4,7] and PEKKA RAATIKAINEN[1]

[1]*Heart and Lung Center, Helsinki University Central Hospital and Helsinki University, Helsinki, Finland;*
[2]*Heart Hospital, Tampere University Hospital, University of Tampere, Tampere, Finland;*
[3]*Department of Oncology, Tampere University Hospital, Tampere, Finland;*
[4]*Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;*
[5]*Faculty of Social Sciences, Tampere University, Tampere, Finland;*
[6]*Department of Surgery, Seinäjoki Central Hospital, Seinäjoki, Finland;*
[7]*Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland*

Abstract. *Background/Aim: Radiotherapy (RT) induces late changes in all cardiac structures. Most studies of early changes focus on individual parameters. Patients and Methods: Data from eighty early-stage breast cancer patients at baseline, post-RT and three-year follow-up visit were assessed prospectively. Changes in ten cardiac parameters were collected including electrocardiogram (ECG), echocardiography, and biomarkers. A percentage of abnormal changes was calculated. Results: The mean heart radiation dose (Dmean) was independently associated with the increased incidence of changes post-RT (β=0.403, p<0.001) and at the three-year follow-up (β=0.353, p=0.001). Each 1-Gray increase in Dmean increased the cardiac changes by 3.7% (95%CI=1.9-5.6%) after RT and 3.1% (95%CI=1.3, 4.9%) at the three-year follow-up. Conclusion: A higher cardiac radiation dose was independently associated with a higher incidence of changes in cardiac parameters. Multiparameter changes imply that the early phase after RT is already characterized by several overlapping cardiac changes.*

Correspondence to: Suvi Sirkku Tuohinen, Heart and Lung Center, Helsinki University Central Hospital and Helsinki University, PO Box 340, 00029 Helsinki, Finland. Tel: +35 8504270565, e-mail: suvi.tuohinen@hus.fi

Key Words: Breast cancer, radiotherapy, cardiac biomarkers, ECG, echocardiography.

Radiotherapy (RT) is an essential part of cancer therapy for approximately half of patients (1, 2). Adverse effects on healthy tissue are the major limiting factor, and they are actively reduced by advances in treatment planning and protective shielding (2). Despite the use of protective measures, cardiac exposure is unavoidable in chest RT due to RT field proximity and radiation scattering. As radiation can affect all layers of cardiac tissue, overlap of multiple pathologies is common (3-6). Taking this into account, one would expect to find multiple cardiac changes even in the early phase after RT.

We have previously reported changes in cardiac biomarkers, electrocardiogram (ECG), and echocardiography after breast cancer RT (7-15). Even though the changes are evident after RT, an independent dose-dependent association has rarely been reported. The aims of this study were to examine whether a multiparameter approach combining these findings would have closer association with radiation dose, and to create a more holistic understanding of the heart following early-stage breast cancer RT. Furthermore, our aims were to clarify which of these parameters had the closest association with RT cardiac doses and to further clarify the development of these changes during the first three years after RT.

Patients and Methods

Patient selection. Patient recruitment for this single-center three-year prospective observational study started in June 2011 and the three-year follow-up ended in June 2016. Eighty patients were recruited: twenty patients with right-sided breast cancer and sixty patients with left-sided breast cancer. Patients were treated with adjuvant RT only, as there was no need for chemotherapy due to their tumor characteristics. The inclusion and exclusion criteria have

Table I. *Cardiac variables used for the analysis in this study.*

Variable name	Early	Late
	Baseline – 3 Days after RT	Baseline – 3 Years after RT
CVIBS	Worsening from baseline to post-RT	Worsening from baseline to 3Y
IBS	Worsening from baseline to post-RT	Worsening from baseline to 3Y
ST2	An increase from baseline value to post-RT	An increase from baseline value to 3Y
ECG	A new T-wave inversion in at least one lead post-RT	Persistent new T-wave inversion at 3Y
GLS	Relative worsening of ≥15% from baseline to post-RT	Relative worsening of ≥15% from baseline to 3Y
Global e	A new global e value <1 1/s at post-RT	A new global e value <1 1/s at 3Y
TAPSE	A decrease of at least 4 mm from baseline to post-RT	A decrease of at least 4 mm from baseline to 3Y
Tn	Troponin T increase by at least 30% from baseline to post-RT	Troponin T above reference level during the follow-up period
Diastolic grade	Worsening from baseline to post-RT	Worsening from baseline to 3Y
proBNP	A new abnormal proBNP value post-RT	A new abnormal proBNP value at 3Y

RT: Radiotherapy; IBS and CVIBS: integrated backscatter and cyclic variation of the IBS; 3Y: three-year follow-up visit; ECG: electrocardiogram; GLS: global longitudinal strain; Global e: global early diastolic strain rate derived from left ventricular speckle tracking analysis; TAPSE: tricuspid annular plane systolic excursion; Tn: Troponin T; proBNP: pro-B-type natriuretic peptide.

been published previously. Briefly, eligible female patients between 18 and 80 years old with early-stage breast cancer were recruited unless they had other malignancies, severe lung disease or significant heart disease (11). The study complied with the Helsinki Declaration, and the local ethics committee approved the protocol. All participants signed an informed consent form before enrollment.

Cardiac variables. A total of 10 biochemical, ECG and echocardiographic parameters were included in this multiparameter analysis. More detailed information on the measurements can be found in our previous publications (7-15). All parameters were handled as binomial, that is, either they displayed or not a change after RT (Early) or at three-year follow-up (Late). The included parameters and the criteria to be defined as changed are shown in Table I.

Threshold definition. The threshold for global longitudinal strain (GLS) change was chosen based on a clinically significant relative decline by 15%, and a global e under one 1/s as this threshold has been published as being clinically significant (16, 17). For troponin T (Tn) we used a 30% increase from baseline to post-RT control, as this was used in our previous publication and there was only one patient with a Tn increase above the threshold level in the early phase (8). However, a value above the reference level was chosen as the threshold in the follow-up thereafter, and elevated pro-B-natriuretic peptide (proBNP) above the clinical reference level was used in both the Early and Late phases. Furthermore, a clear and distinct change in an ECG feature was chosen to represent a change after RT, namely a novel T-wave inversion after baseline ECG (13). For tricuspid annular plane systolic excursion (TAPSE), such a change was a more than 4 mm decrease from baseline (9). However, for parameters such as integrated backscatter (IBS), cyclic variation of integrated backscatter (CVIBS), and ST2, there are no commonly used thresholds, and a worsening from baseline was used instead. Likewise, a minimum of worsening by one diastolic grade was used to define a change in diastology.

Combination of parameters. For each individual, a percentage of abnormal changes was calculated in the ten parameters early after RT ($Early_{combination}$) and at the three-year follow-up ($Late_{combination}$). As some of the parameters clearly peaked in the early phase, while others peaked in the late phase, a $Best_{combination}$ was developed using the best combination of the early and late peaking parameters. $Best_{combination}$ included ECG and IBS in the early phase and Tn, proBNP, global e, CVIBS, and ST2 in the late phase. GLS15, TAPSE and diastolic grade were left out of $Best_{combination}$ as they did not seem to contribute to the overall results in either phase.

Statistics. The data are presented as the means with standard deviations (SD) for variables with normal distributions, as medians with quartiles for nonnormally distributed variables and as numbers with percentages for categorical variables. The chi-square test or Fisher's test was used for categorical associations of the cardiac variables with a mean heart dose (Dmean) >2 Gy and maximal heart dose (Dmax) >40 Gy. Receiver operator curve (ROC) analysis was used to test categorical cardiac parameters with Dmean and Dmax. In the ROC curves, the true positives are plotted against the false positives for different cutoff points of the Early, Late and Best combinations using the cutoff value of 2 Gy for Dmean and the cutoff value of 40 Gy for Dmax. An independent T test was used to test the differences in Dmean and Dmax for those parameters with significant area under the curves (AUC). A multivariable analysis was performed using stepwise linear regression analysis. The included covariates were the Dmean, age at inclusion, no other concurrent disease, smoking status, hypertension, and use of aromatase inhibitor. All *p*-values are two-sided and a *p*-value <0.05 was considered indicative of statistical significance. The analysis was performed with IBM SPSS Statistics Version 25.

Results

The general characteristics of the study population are shown in Table II. All patients completed the three-year follow-up. There were seven hospitalizations due to cardiac causes: three patients were hospitalized due to atrial fibrillation, one patient underwent catheter ablation of atrioventricular nodal

Table II. *Baseline characteristics*.

	n/med	(%)/[Q1,Q3]
Age (years)	64	[58, 67]
BMI (kg/m^2)	26.4	[24.3, 30.0]
BSA (m^2)	1.77	[1.69, 1.93]
Hypertension	35	(44%)
Never smoker	20	(25%)
No other concurrent diagnosis	10	(13%)
Breast cancer, right/left-sided	20/60	(25%/75%)
Breast cancer treatment		
Chemotherapy	0	(0%)
Aromatase inhibitor	27	(36%)
Radiotherapy	100	(100%)
Radiotherapy doses		
Mean heart dose (Gy)	2.16	[0.87, 3.74]
Max heart dose (Gy)	45.9	[8.0, 48.1]

BMI: Body mass index; BSA: body surface area; Gy: gray.

reentrant tachycardia, one patient received a pacemaker due to second-degree Mobitz 2 AV nodal block, and two patients were hospitalized due to worsening of pre-existing coronary artery disease and aortic stenosis. There was no cancer recurrence or death during the follow-up period.

Changes in individual markers. The number of abnormal findings among the cardiac parameters for each patient is displayed in Figure 1. Missing values accounted for 5.9% and 3.8% of all parameters after RT and at the three-year follow-up, respectively. Missing values were most commonly observed for ST2 analysis accounting for 16% of the total data points, while there were no missing values among Tn, proBNP or diastolic grade values.

The median [Q_1, Q_3] percentage of cardiac changes per patient was 30% [20, 40] at the post-RT control and 30% [20, 40] at the three-year follow-up. The distribution of the changes is illustrated in Figure 2. The results of chi-square analysis for each cardiac parameter and Dmean with a 2 Gy treshold is shown in Table III, and those for Dmax with a 40 Gy threshold are shown in Table IV. In addition, the ROC results for each individual cardiac parameter and Dmean and Dmax are shown in Table V. Considering the significant associations, there were differences between the parameters. IBS seemed to peak early, and global e and ST2 peaked late, while CVIBS, Tn, ECG, and proBNP were equally present in both early and late phase. In contrast, TAPSE, GLS15 and diastolic grade did not show significant associations at any follow-up visit.

CVIBS. The Dmean values of patients with and without CVIBS worsening were 2.4 [1.1, 3.9] Gy and 1.5 [0.6, 1.8] Gy (p=0.014) at the Early follow-up, and 2.2 [1.3, 3.9] Gy and 1.5 [0.6, 2.5] Gy (p=0.019) at the Late follow-up, respectively. Likewise, the Dmax values of patients with and without CVIBS worsening were 46.2 [14.6, 48.5] Gy and 43.4 [5.0, 46.3] Gy (p=0.216) at the Early follow-up and 46.4 [19.1, 48.5] and 41.3 [4.6, 46.0] (p=0.087) at the Late follow-up, respectively.

IBS. The Dmean values of patients with and without IBS worsening at the Early follow-up were 2.4 [1.4, 3.8] Gy and 1.4 [0.6, 2.3] Gy (p=0.022), respectively. The Dmax values of patients with and without IBS worsening at the Early follow-up were 46.4 [8.1, 48.4] Gy and 43.0 [4.8, 46.8] Gy (p=0.224), respectively.

ST2. The Dmean values of patients with and without an ST2 increase at the Late follow-up were 2.2 [1.4, 4.0] Gy and 1.8 [0.7, 3.2] Gy (p=0.162), respectively. The Dmax values of patients with and without an ST2 increase at the Late follow-up were 46.5 [29.4, 48.4] Gy and 44.2 [5.1, 46.6] Gy (p=0.087), respectively.

ECG. The Dmean values for those with and without a T-inversion at the Early follow-up were 3.5 Gy [2.2, 4.9] Gy, and 1.6 [0.6, 3.2] Gy (p<0.001), respectively. Likewise, the Dmax values for patients with and without T-wave inversion after RT were 47.3 [45.9, 49.0] Gy and 43.2 [5.0, 47.3] Gy (p<0.001), respectively. At the Late follow-up, the Dmean values of patients with and without a persistent T-wave inversion were 4.4 [3.4, 5.6] Gy and 2.0 [0.8, 3.5] Gy (p=0.005), respectively, while the Dmax values of patients with and without a persistent T-wave inversion were 48.2 [45.8, 51.3] Gy and 45.9 [7.9, 47.6] Gy (p=0.280), respectively.

Global e. The Dmean values of patients with and without a depressed global e were 4.4 [3.4, 5.6] Gy versus 2.0 [0.8, 3.5] Gy (p=0.018) at the Late follow-up, respectively. Likewise, the Dmax values of patients with and without a depressed Global e were 48.2 [45.8, 51.3] Gy and 45.9 [7.9, 47.6] Gy (p=0.014), respectively.

Tn. The Dmean values of those with and without a Tn change at the Early follow-up were 3.5 [2.1, 4.3] Gy and 1.9 [0.7, 3.5] Gy (p=0.025), respectively. Likewise, the Dmax values of patients with and without a Tn change at the Early follow-up were 47.2 [45.8, 49.2] Gy and 45.0 [6.1, 47.4] Gy (p=0.012), respectively. At the Late follow-up, the Dmean values of patients with and without a Tn change were 4.4 [3.4, 5.6] Gy and 2.0 [0.8, 3.5] Gy (p=0.002), respectively. The Dmax values at the Late follow-up of patients with and without a Tn change were 48.2 [45.8, 51.3] Gy and 45.9 [7.9, 47.6] Gy (p=0.038), respectively.

ProBNP. The Dmean values of those with and without abnormal proBNP at the Early follow-up were 4.2 [2.3, 5.0] Gy and 2.0 [0.8, 3.6] Gy (p=0.112), respectively. Likewise,

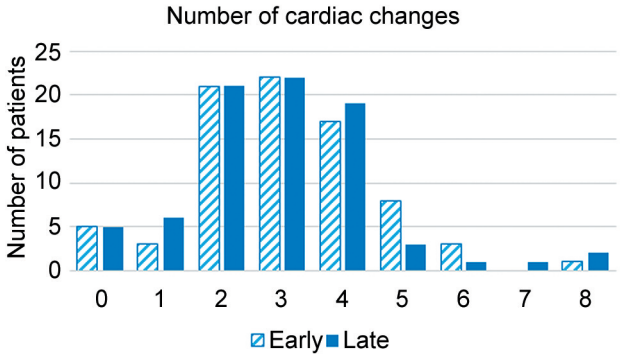

Figure 1. *Number of cardiac changes at the Early and Late follow-ups. The distributions of early (dashed) and late (blue) changes are shown on the y-axis. The height of the columns indicates the number of patients with the respective number of changes.*

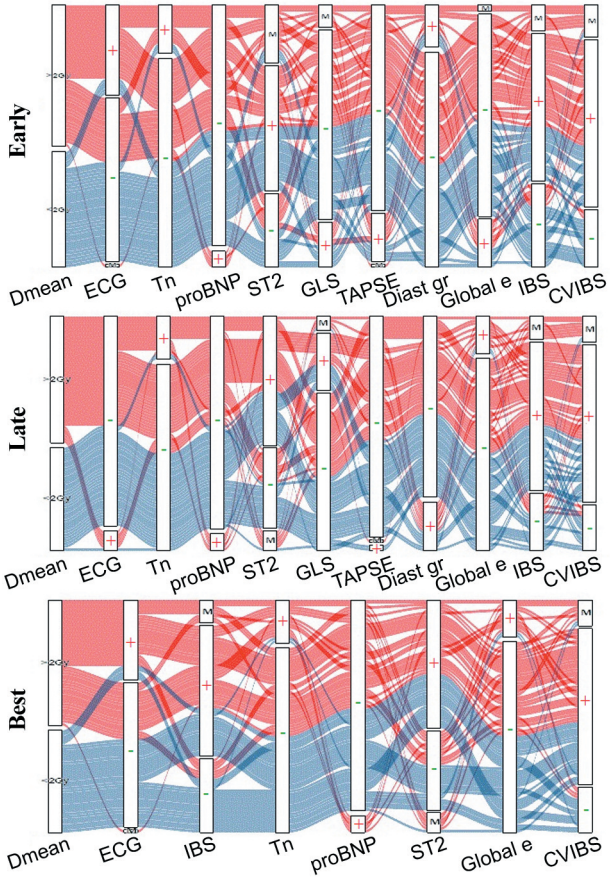

Figure 2. *Cardiac changes according to a 2 Gy mean heart dose (Dmean) illustrated as an Alluvian diagram. The top row represents changes after radiotherapy (Early), middle row shows changes at three-year follow-up (Late), and bottom row displays the best combination of changes (Best). The first column on the left represents Dmean: red color illustrates Dmean >2 Gy and blue color Dmean <2 Gy.*

the Dmax values of patients with and without abnormal proBNP after RT were 46.8 [45.8, 54.6] Gy and 45.9 [7.8, 48.1] Gy (p=0.002), respectively. At the Late follow-up, the Dmean values of patients with and without an abnormal proBNP value were 3.9 [2.8, 5.8] Gy and 2.0 [0.8, 3.6] Gy (p=0.018), respectively. The Dmax values of patients with and without an abnormal proBNP value were 46.7 [36.8, 52.3] Gy and 45.9 [7.7, 48.1] Gy (p=0.284), respectively.

Analysis of combined changes. The median [Q1, Q3] change in $Early_{combination}$ was 30.0% [20, 40], $Late_{combination}$ 30.0% [20.0, 40.0], and $Best_{combination}$ 28.6% [14.3, 42.9]. The number of patients with no changes was 5 (6.3%), 5 (6.3%) and 7 (8.8%) for $Early_{combination}$, $Late_{combination}$ and $Best_{combination}$, respectively. A change in at least half of the parameters was observed in 15 patients (18.8%) at the post-RT follow-up ($Early_{combination}$), in eight patients (10%) at the three-year follow-up ($Late_{combination}$), and in 13 patients (16.3%) using the $Best_{combination}$.

Figure 3 displays the ROC curves for Dmean with a 2 Gy threshold and Dmax with a 40 Gy threshold: the AUC values of $Early_{combination}$ were 0.749 [95%CI=0.731-0.917] (p<0.001) and 0.726 [95%CI=0.618-0.834] (p=0.001), respectively. Likewise, the AUC values of Dmean with a 2 Gy threshold and Dmax with a 40 Gy threshold for $Late_{combination}$ were 0.711 [95%CI=0.579-0.824] (p=0.001) and 0.645 [95%CI=0.523-0.768] (p=0.038), respectively. Finally, the AUC values of Dmean with a 2 Gy threshold and Dmax with a 40 Gy threshold for $Best_{combination}$ were 0.824 [95%CI=0.731-0.917] (p<0.001) and 0.744 [95%CI=0.633-0.855] (p=0.001), respectively.

A scatter dot illustration of the associations of combination changes with Dmean and Dmax is shown in Figure 4 and a scatter dot illustration of the associations between combination changes and age is displayed in Figure 5. Multivariable analysis including Dmean, age at inclusion, no other concurrent disease, smoking status, hypertension, and use of aromatase inhibitors was performed. Independent associations of Dmean and age with all combinations were found. Dmean was independently associated with $Early_{combination}$ (β=0.403, p<0.001), $Late_{combination}$ (β=0.353, p=0.001) and $Best_{combination}$ (β=0.558, p<0.001). Each 1-Gray increase in Dmean increased $Early_{combination}$ by 3.7% [95%CI=1.9, 5.6], $Late_{combination}$ by 3.1% [95%CI=1.3-4.9] and $Best_{combination}$ by 5.9% [95%CI=4.0, 7.9].

Higher age at the time of RT was also independently associated with all combinations: $Early_{combination}$ (β=0.294, p=0.004), $Late_{combination}$ (β=0.230, p=0.029) and $Best_{combination}$ (β=0.216, p=0.020). Each 1-year increase in age at the time of RT increased the incidence of changes by 0.7% [95%CI=0.3-1.3] in $Early_{combination}$, by 0.6% [95%CI=0.1-1.1] in $Late_{combination}$ and by 0.6% [95%CI=0.1-1.2] in $Best_{combination}$.

Table III. *Chi-square analysis of the associations between individual cardiac parameters and Dmean with a 2 Gy threshold.*

	Post-RT					Three-year follow-up				
	Dmean					Dmean				
	<2 Gy		≥2 Gy			<2 Gy		≥2 Gy		
Cardiac changes	n	%	n	%	*p*-Value	n	%	n	%	*p*-Value
CVIBS	19	55.9	33	91.7	**0.001**	22	64.7	33	89.2	**0.014**
IBS	17	47.2	29	80.6	**0.003**	23	63.9	29	80.6	0.114
ST2	20	62.5	19	63.3	0.946	19	54.3	26	68.4	0.215
ECG	5	13.9	23	53.5	**<0.001**	1	2.8	6	13.6	0.122
GLS15	7	19.4	7	18.9	0.955	9	25.7	11	27.5	0.861
Global e	6	16.7	9	21.4	0.595	2	5.6	11	25.0	**0.019**
TAPSE	6	16.7	9	20.9	0.630	2	5.6	0	0.0	0.117
Tn	3	8.3	12	27.3	**0.031**	2	5.6	13	29.5	**0.006**
Diastolic grade	4	11.1	9	20.5	0.260	7	19.4	10	22.7	0.721
proBNP	0	0.0	5	11.4	0.061	0	0.0	6	13.6	**0.030**

Dmean: Mean heart radiation dose; Gy: Gray; RT: radiotherapy; IBS and CVIBS: integrated backscatter and cyclic variation of IBS; ECG: electrocardiogram; GLS15: a 15% relative decrease in global longitudinal strain; Global e: global early strain rate derived from left ventricular speckle tracking analysis; TAPSE: tricuspid annular plane systolic excursion; Tn: troponin T; proBNP: pro-B-type natriuretic peptide. Significant *p*-Values are shown in bold.

Table IV. *Chi-square analysis of the associations between individual cardiac parameters and Dmax with a 40 Gy threshold.*

	Post-RT					Three-year follow-up				
	Dmax					Dmax				
	<40 Gy		≥40 Gy			<40 Gy		≥40 Gy		
Cardiac changes	n	%	n	%	*p*-Value	n	%	n	%	*p*-Value
CVIBS	15	65.2	37	78.7	0.225	15	65.2	40	83.3	0.087
IBS	14	56.0	32	68.1	0.309	19	76.0	33	70.2	0.602
ST2	15	71.4	24	58.5	0.320	12	50.0	33	67.3	0.152
ECG	1	4.2	27	49.1	**<0.001**	1	4.0	6	10.9	0.425
GLS15	3	12.0	11	22.9	0.354	6	25.0	14	27.5	0.823
Global e	2	8.0	13	24.5	0.124	1	4.0	12	21.8	0.054
TAPSE	5	20.8	10	18.2	0.764	2	8.0	0	0.0	0.090
Tn	2	8.0	13	23.6	0.128	2	8.0	13	23.6	0.128
Diastolic grade	3	12.0	10	18.2	0.745	3	12.0	14	25.5	0.173
proBNP	0	0.0	5	9.1	0.318	1	4.0	5	9.1	0.660

Dmax: Maximum heart radiation dose; Gy: Gray; RT: radiotherapy; IBS and CVIBS: integrated backscatter and cyclic variation of IBS; ECG: electrocardiogram; GLS15: a 15% relative decrease in global longitudinal strain; Global E: global early strain rate derived from left ventricular speckle tracking analysis; TAPSE: tricuspid annular plane systolic excursion; Tn: troponin T; proBNP: pro-B-type natriuretic peptide. Significant *p*-Values are shown in bold.

Discussion

This study shows that the early phase after chest RT is characterized by multiple simultaneous cardiac changes and that the combination of changes was independently associated with cardiac radiation doses. This is in line with the late clinical manifestation of multiple overlapping cardiac changes (6, 16).

Radiotherapy-induced adverse cardiac effects. RT initiates tissue changes via direct cellular damage and activation of radical oxygen species (18). The early phase occurs from

Table V. *Area under the curve values for cardiac parameters in the early and late phases versus mean and max heart radiation doses.*

	Mean heart dose			Max heart dose		
	AUC	95%CI	*p*-Value	AUC	95%CI	*p*-Value
Early changes						
CVIBS	0.688	[0.553, 0.823]	**0.018**	0.650	[0.516, 0.784]	0.060
IBS	0.677	[0.564, 0.808]	**0.013**	0.645	[0.515, 0.774]	**0.043**
ST2	0.486	[0.333, 0.639]	0.855	0.517	[0.364, 0.670]	0.821
ECG	0.780	[0.680, 0.881]	**<0.001**	0.731	[0.621, 0.841]	**0.001**
GLS15	0.550	[0.407, 0.694]	0.561	0.531	[0.390, 0.673]	0.716
Global e	0.582	[0.429, 0.736]	0.326	0.552	[0.408, 0.697]	0.530
TAPSE	0.496	[0.325, 0.668]	0.965	0.521	[0.336, 0.706]	0.803
Tn	0.681	[0.535, 0.826]	**0.030**	0.678	[0.542, 0.813]	**0.032**
Diast. grade	0.577	[0.383, 0.771]	0.383	0.522	[0.353, 0.691]	0.799
proBNP	0.751	[0.591, 0.911]	0.062	0.691	[0.512, 0.869]	0.155
Late changes						
CVIBS	0.676	[0.533, 0.818]	**0.033**	0.693	[0.561, 0.825]	**0.019**
IBS	0.582	[0.388, 0.669]	0.711	0.588	[0.460, 0.715]	0.253
ST2	0.608	[0.473, 0.743]	0.123	0.637	[0.506, 0.767]	0.051
ECG	0.785	[0.589, 0.980]	**0.013**	0.710	[0.489, 0.932]	0.067
GLS15	0.525	[0.382, 0.667]	0.746	0.520	[0.380, 0.660]	0.792
Global e	0.699	[0.556, 0.842]	**0.024**	0.661	[0.526, 0.796]	0.067
TAPSE	0.136	[0.000, 0.302]	0.081	0.110	[0.000, 0.242]	0.061
Tn	0.735	[0.600, 0.871]	**0.005**	0.677	[0.538, 0.816]	**0.033**
Diast. grade	0.561	[0.403, 0.720]	0.441	0.542	[0.394, 0.691]	0.593
proBNP	0.784	[0.504, 0,834]	**0.021**	0.609	[0.418, 0.800]	0.290

CI: Confidence interval; AUC: area under the curve; IBS and CVIBS: calibrated integrated backscatter value from the septum and cyclic variation of the IBS; ECG: a new T-wave inversion after baseline in the electrocardiogram; GLS15: a relative decrease of 15% in the global longitudinal strain; Global e: early strain rate value derived from left ventricular speckle tracking analysis; TAPSE: tricuspid annulus plane systolic excursion; Tn: Troponin T; Diast. grade: worsening of the diastolic grade after baseline; proBNP: a new abnormal value of pro-B-type natriuretic peptide after baseline. Significant *p*-Values are shown in bold.

minutes to days after radiation and is characterized by inflammatory tissue changes (19-21). The inflammatory phase triggers a complex cascade, which is not fully understood. The cascade includes endothelial damage, capillary thrombosis and perivascular fibrosis, and it leads to vascular changes and diffuse fibrosis in the long term (16, 18-20, 22). The early inflammatory phase is usually silent in the heart due to lower heart exposure with modern heart-sparing programs. Clinically overt manifestations usually appear with several years of latency and are caused by the slow accumulation of fibrotic and sclerotic cardiac changes. The clinical manifestations may include stenotic lesions in the small and large arteries, valvular lesions, myocardial fibrotic changes with the development of heart failure with preserved ejection fraction (HFpEF), constriction, arrythmia, and conduction problems (2, 6, 16). These manifestations often overlap and patients are prone to present with more than one cardiac manifestation (3, 16). Chest RT increases late mortality by 2 to 6-fold, and in some patient groups, late cardiac mortality exceeds cancer mortality (16, 23).

Multiparameter changes in this study. RT induces cardiac changes, which are initiated at the time of RT and develop slowly thereafter. As the late changes are multiple, overlapping late manifestations, one would suppose that the early manifestations would present the same pancardiac character. The aim of this study was to assess whether such manifestation with multiple changes would occur in the early phase. By combining ten variables shown to change after RT in our previous publications, a clear and independent association with RT dose was found. A higher Dmean and Dmax induced a higher frequency of cardiac changes in a dose-dependent manner. Using the best combination of parameters, each 1-Gy increase in Dmean induced a 5.9% (95%CI=4.0-7.9%) increase in changes in cardiac parameters. Although the relationship between the early subclinical changes and late clinically significant manifestations is a matter of debate, it is interesting that the magnitude of changes induced by each 1-Gy increase in Dmean is similar to late RT-induced clinical damage. Sardano *et al.* showed that each 1-Gy increase in Dmean increased the risk of late RT-induced heart disease by 4% (24). Likewise, in a study by Darby *et al.*, each 1-Gy increase in Dmean increased the risk of ischemic coronary artery disease by 7.4% (25).

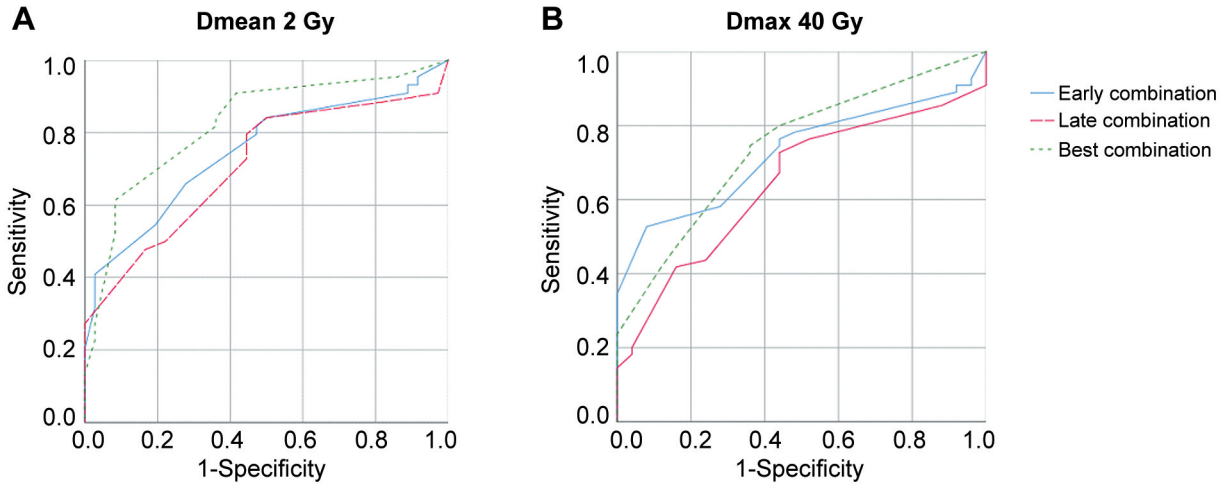

Figure 3. *Receiver operator curve for mean heart dose over 2 Gy (A) and maximum heart dose over 40 Gy (B). (A) The best combination (dashed blue line) has the largest area under the curve 0.807 (p<0.001), while early combination (solid blue line) and late combination (dashed red line) have 0.760 (p<0.001) and 0.703 (p=0.002), respectively. (B) The best, early and late combinations have an area under the curve of 0.744 (p=0.001), 0.726 (p=0.001), and 0.645 (p=0.038), respectively.*

The clear dose-dependency revealed by a multiparameter approach in this study implies that a combination of parameters might indicate better overall cardiac exposure than individual parameters. It may be that individual susceptibility makes one patient more prone to present certain changes and another patient more likely to present other changes. A multiparameter approach overcomes such individual variation and might therefore be a more robust indicator of RT-induced cardiac effects.

Early radiotherapy-induced changes. Both $Early_{combination}$ and $Late_{combination}$ were associated with Dmean and Dmax. However, there were differences in individual parameters that peaked in the early phase and at the three-year follow-ups, probably reflecting differences in the RT-induced tissue changes. As the early phase after RT is characterized by inflammatory tissue changes, such inflammatory changes might at least partially explain early-peaking cardiac changes such as T-wave inversion on ECG and increasing tissue density measured by IBS in this study. The exact mechanism of T-wave inversions is not well understood. In previous studies, an increase and subsequent decrease in myocardial IBS values have been observed in situations with tissue inflammatory changes such as allograft rejection, transient kidney dysfunction and changes seen in postmenopausal therapy (26-28). Therefore, tissue inflammatory changes may have caused an initial increase in IBS values.

Late radiotherapy-induced changes. There was no clear peak in the number of patients with changes in the individual parameters at the three-year follow-up, but rather a modest increase in changes in cardiac biomarkers and echocardiography measurements. A gradual increase in the frequency of cardiac changes complies with the slow development of RT-induced fibrotic changes. Parameters associated with radiation dose at the three-year follow-up might serve as surrogate markers of the slowly evolving fibrotic process, especially late peak global e. Similar changes after RT were discovered in a study by Sirtrahan *et al*. (29). Such diastolic changes might lead to impaired left ventricular filling and to HFpEF. In fact, Saiki *et al*. have reported increased risk of HFpEF as early as 5.8 years after RT (30).

Other considerations. Data from others and our previous publications show that GLS, TAPSE, and diastolic grade are worsened by chest RT (9, 11, 14, 15, 29, 31-33). However, in this study, these parameters performed worse than others with regard to the association with heart radiation doses. This might be due to the dichotomization of the parameter with a subsequent reduction in information. Furthermore, important regional data are not apparent managing data in this way.

Seven of our patients were hospitalized for cardiac reasons during the follow-up period. As the follow-up was only three years and given the variety of cardiac reasons for hospitalization, a causal link between RT and hospitalizations was considered unlikely.

Clinical implications. There are several clinical implications of our study. First, the results of this study imply that RT-induced cardiac changes initially resemble pancardiac nature, and use of a multiparameter approach might be a

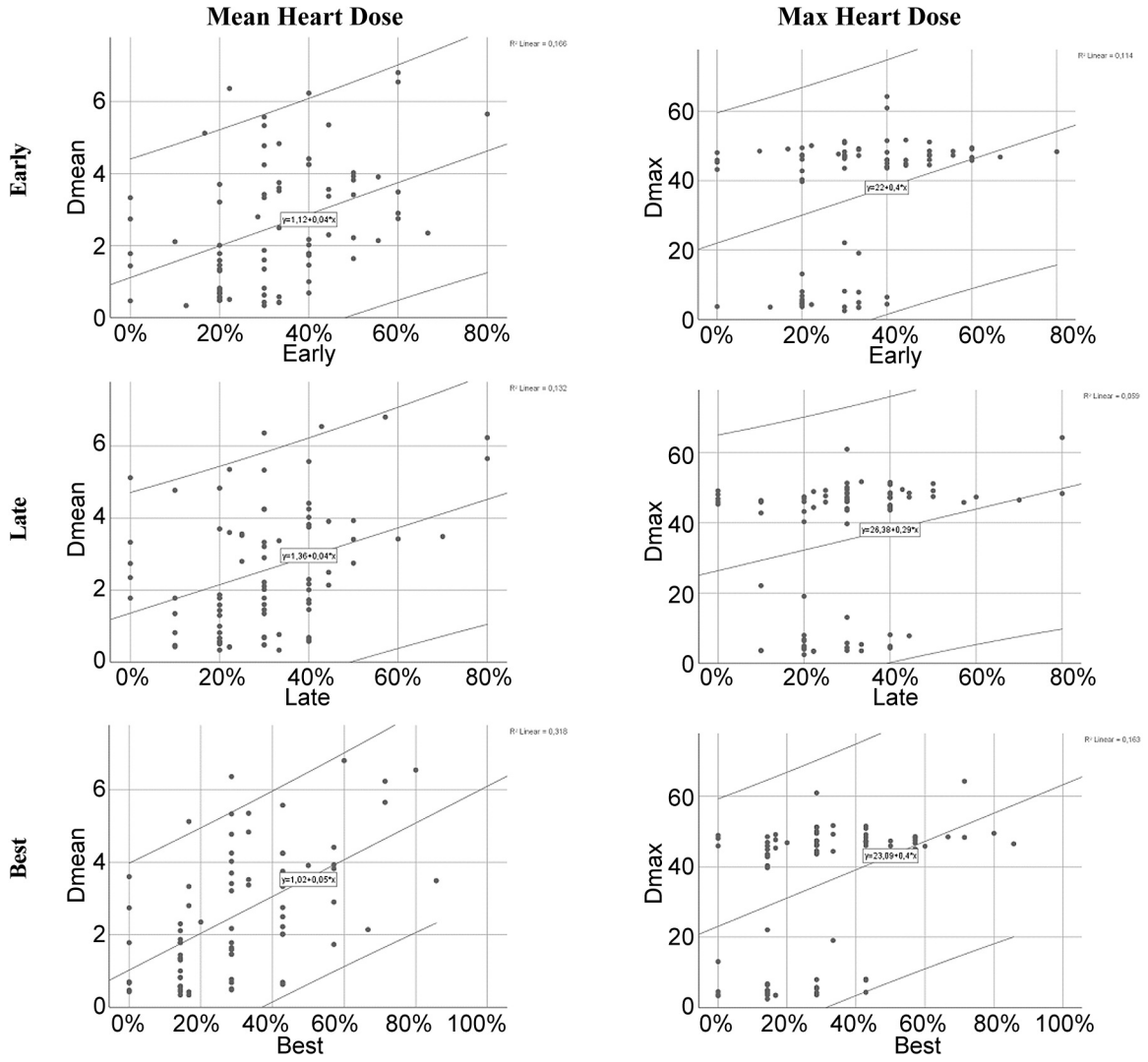

Figure 4. *Scatter dot plots: heart radiation doses and cardiac changes. The top row represents Early$_{combination}$, the middle row Late$_{combination}$, and the bottom row Best$_{combination}$. The mean heart dose is illustrated in the left column and the maximum heart dose is illustrated in the right column.*

better way to reveal individual impacts. Second, this study clarifies which tools are most appropriate to detect early and late cardiac changes. This could help clinicians and scientists choose the most appropriate tool for screening in cases where a multiparameter approach is not practical. Third, our study might provide us with a better understanding of the changes in these cardiac parameters that present after RT. As tissue samples have shown early changes to be characterized by inflammatory changes and late changes to present accumulation of diffuse fibrosis and sclerotic changes, it may be concluded that early T-wave inversions and changes in IBS are associated with inflammatory tissue changes whereas global e might present an accumulation of myocardial fibrosis.

Overall, a multiparameter approach used to study radiotherapy-induced myocardial changes showed a close relationship with cardiac radiation doses and revealed a multichange nature of cardiac parameters even in the early phases after radiotherapy.

Limitations. The most important limitation of our study is the short follow-up time. As clinically significant cardiac adverse effects appear with several years of latency, it is unclear whether a multiparameter approach is a more valid way to predict late adverse events than an approach that considers changes in individual parameters. A longer follow-up of this patient population is ongoing to clarify this important aspect. Furthermore, the study population was rather small, but this

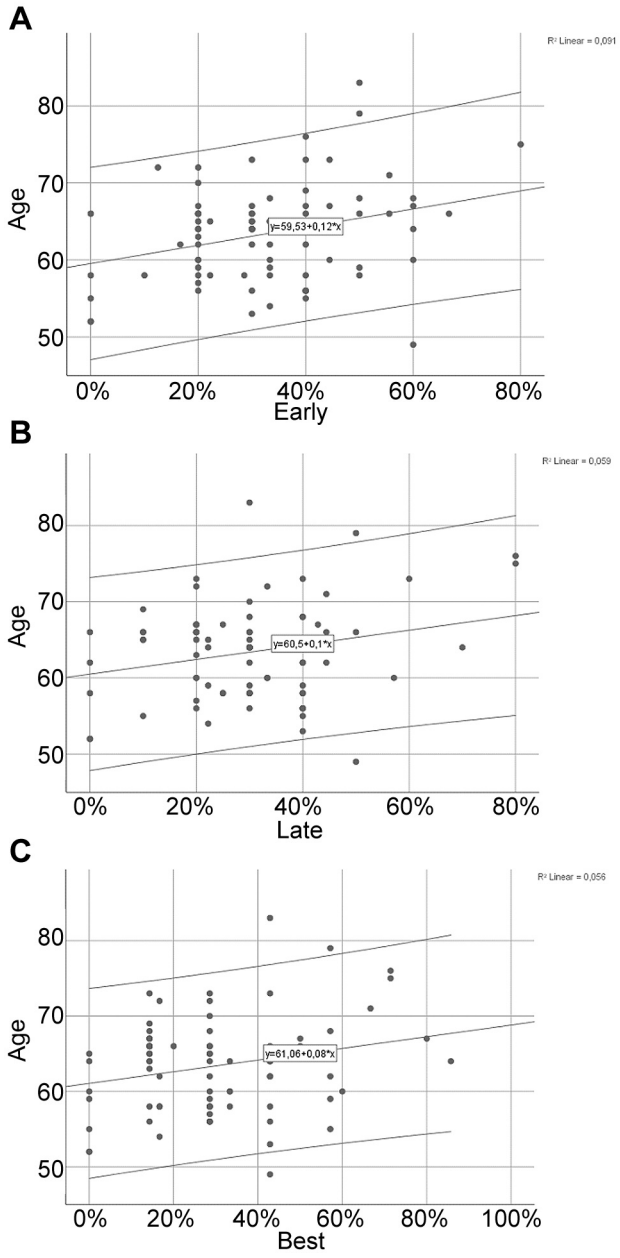

Figure 5. *Scatter dot plots: age at the time of radiation therapy and cardiac changes. The top image is for* $Early_{combination}$*, the middle image is for* $Late_{combination}$*, and the bottom image is for* $Best_{combination}$*.*

was a result of balancing meticulous study protocols with a larger population size. In addition, for each cardiac parameter, a cutoff point was chosen. For several parameters a clear clinical cutoff was used, but for many parameters in research use only, there were no such cutoff values. For this reason, cutoff values were defined according to best judgement, but cutoff values other than those chosen here might have performed better or worse. Finally, with longer follow-up times, many patients may experience cardiac events unrelated to RT that influence cardiac parameters. Our analysis did not include such factors. However, in such cases a multiparameter approach might overcome such confounding factors better than single-parameter analysis.

Conclusion

A multiparameter approach to reveal early RT-induced cardiac changes is feasible and resembles pancardiac from early on. Cardiac radiation doses were independently associated with cardiac changes, with each 1-Gy of Dmean increasing cardiac changes by 3.7% post-RT and 3.1% at the three-year follow-up.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare.

Authors' Contributions

All the Authors have contributed significantly to the concept design of this manuscript, and the work leading to the final manuscript. All Authors have reviewed the article and agreed with its content.

Acknowledgements

This study was supported by nonprofit trusts: Paavo and Eila Salonen Legacy, Aarne Koskelo Legacy, Georg and Ella Ehrnroot Trust and Competitive State Reseach Financing of the Expert Responsibility area of Tampere University Hospital. The Authors would also like to thank the research nurses Virpi Palomäki, Hanna-Leena Näppilä, Kati Helleharju and Katri Mikkonen for their expert assistance during the study.

References

1 Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD and Burnet NG: Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer *9(2)*: 134-142, 2009. PMID: 19148183. DOI: 10.1038/nrc2587

2 Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J and Mitchell JD: Past, present, and future of radiation-induced cardiotoxicity: refinements in targeting, surveillance, and risk stratification. JACC CardioOncol *3(3)*: 343-359, 2021. PMID: 34604796. DOI: 10.1016/j.jaccao.2021.06.007

3 Bonou M, Masoura C, Kapelios CJ and Barbetseas J: Radiation-induced 'pancarditis'. Age Ageing *49(5)*: 889-890, 2020. PMID: 32603409. DOI: 10.1093/ageing/afaa074

4 Nielsen KM, Offersen BV, Nielsen HM, Vaage-Nilsen M and Yusuf SW: Short and long term radiation induced cardiovascular disease in patients with cancer. Clin Cardiol *40(4)*: 255-261, 2017. PMID: 28139844. DOI: 10.1002/clc.22634

5 Koutroumpakis E, Palaskas NL, Lin SH, Abe JI, Liao Z, Banchs J, Deswal A and Yusuf SW: Modern radiotherapy and risk of cardiotoxicity. Chemotherapy *65(3-4)*: 65-76, 2020. PMID: 33049738. DOI: 10.1159/000510573

6 Mitchell JD, Cehic DA, Morgia M, Bergom C, Toohey J, Guerrero PA, Ferencik M, Kikuchi R, Carver JR, Zaha VG, Alvarez-Cardona JA, Szmit S, Daniele AJ, Lopez-Mattei J, Zhang L, Herrmann J, Nohria A, Lenihan DJ and Dent SF: Cardiovascular manifestations from therapeutic radiation: a multidisciplinary expert consensus statement from the International Cardio-Oncology Society. JACC CardioOncol *3(3)*: 360-380, 2021. PMID: 34604797. DOI: 10.1016/j.jaccao.2021.06.003

7 Aula H, Skyttä T, Tuohinen S, Luukkaala T, Hämäläinen M, Virtanen V, Raatikainen P, Moilanen E and Kellokumpu-Lehtinen PL: ST2 levels increased and were associated with changes in left ventricular systolic function during a three-year follow-up after adjuvant radiotherapy for breast cancer. Breast *49*: 183-186, 2020. PMID: 31862685. DOI: 10.1016/j.breast.2019.12.001

8 Skyttä T, Tuohinen S, Boman E, Virtanen V, Raatikainen P and Kellokumpu-Lehtinen PL: Troponin T-release associates with cardiac radiation doses during adjuvant left-sided breast cancer radiotherapy. Radiat Oncol *10*: 141, 2015. PMID: 26159409. DOI: 10.1186/s13014-015-0436-2

9 Tuohinen SS, Skyttä T, Virtanen V, Luukkaala T, Kellokumpu-Lehtinen PL and Raatikainen P: Early effects of adjuvant breast cancer radiotherapy on right ventricular systolic and diastolic function. Anticancer Res *35(4)*: 2141-2147, 2015. PMID: 25862870.

10 Tuohinen SS, Skyttä T, Virtanen V, Virtanen M, Luukkaala T, Kellokumpu-Lehtinen PL and Raatikainen P: Detection of radiotherapy-induced myocardial changes by ultrasound tissue characterisation in patients with breast cancer. Int J Cardiovasc Imaging *32(5)*: 767-776, 2016. PMID: 26757708. DOI: 10.1007/s10554-016-0837-9

11 Tuohinen SS, Skyttä T, Poutanen T, Huhtala H, Virtanen V, Kellokumpu-Lehtinen PL and Raatikainen P: Radiotherapy-induced global and regional differences in early-stage left-sided *versus* right-sided breast cancer patients: speckle tracking echocardiography study. Int J Cardiovasc Imaging *33(4)*: 463-472, 2017. PMID: 27873127. DOI: 10.1007/s10554-016-1021-y

12 Tuohinen SS, Skyttä T, Huhtala H, Virtanen V, Virtanen M, Kellokumpu-Lehtinen PL and Raatikainen P: Detection of early radiotherapy-induced changes in intrinsic myocardial contractility by ultrasound tissue characterization in patients with early-stage breast cancer. Echocardiography *34(2)*: 191-198, 2017. PMID: 28240428. DOI: 10.1111/echo.13433

13 Tuohinen SS, Keski-Pukkila K, Skyttä T, Huhtala H, Virtanen V, Kellokumpu-Lehtinen PL, Raatikainen P and Nikus K: Radiotherapy-induced Early ECG Changes and Their Comparison with Echocardiography in Patients with Early-stage Breast Cancer. Anticancer Res *38(4)*: 2207-2215, 2018. PMID: 29599341. DOI: 10.21873/anticanres.12463

14 Tuohinen SS, Skytta T, Huhtala H, Virtanen V, Kellokumpu-Lehtinen PL and Raatikainen P: Left ventricular speckle tracking echocardiography changes among early-stage breast cancer patients three years after radiotherapy. Anticancer Res *39(8)*: 4227-4236, 2019. PMID: 31366510. DOI: 10.21873/anticanres.13584

15 Tuohinen SS, Skyttä T, Huhtala H, Poutanen T, Virtanen V, Kellokumpu-Lehtinen PL and Raatikainen P: 3-year follow-up of radiation-associated changes in diastolic function by speckle tracking echocardiography. JACC CardioOncol *3(2)*: 277-289, 2021. PMID: 34396335. DOI: 10.1016/j.jaccao.2021.03.005

16 Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, Cosyns B, Coucke P, Dulgheru R, Edvardsen T, Gaemperli O, Galderisi M, Griffin B, Heidenreich PA, Nieman K, Plana JC, Port SC, Scherrer-Crosbie M, Schwartz RG, Sebag IA, Voigt JU, Wann S, Yang PC, European Society of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance and American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography: Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr *26(9)*: 1013-1032, 2013. PMID: 23998694. DOI: 10.1016/j.echo.2013.07.005

17 Morris DA, Takeuchi M, Nakatani S, Otsuji Y, Belyavskiy E, Aravind Kumar R, Frydas A, Kropf M, Kraft R, Marquez E, Osmanoglou E, Krisper M, Köhncke C, Boldt LH, Haverkamp W, Tschöpe C, Edelmann F, Pieske B and Pieske-Kraigher E: Lower limit of normality and clinical relevance of left ventricular early diastolic strain rate for the detection of left ventricular diastolic dysfunction. Eur Heart J Cardiovasc Imaging *19(8)*: 905-915, 2018. PMID: 28977386. DOI: 10.1093/ehjci/jex185

18 Yarnold J and Brotons MC: Pathogenetic mechanisms in radiation fibrosis. Radiother Oncol *97(1)*: 149-161, 2010. PMID: 20888056. DOI: 10.1016/j.radonc.2010.09.002

19 Cuomo JR, Sharma GK, Conger PD and Weintraub NL: Novel concepts in radiation-induced cardiovascular disease. World J Cardiol *8(9)*: 504-519, 2016. PMID: 27721934. DOI: 10.4330/wjc.v8.i9.504

20 Fajardo LF and Stewart JR: Pathogenesis of radiation-induced myocardial fibrosis. Lab Invest *29(2)*: 244-257, 1973. PMID: 4724850.

21 Westbury CB and Yarnold JR: Radiation fibrosis – current clinical and therapeutic perspectives. Clin Oncol (R Coll Radiol) *24(10)*: 657-672, 2012. PMID: 22608361. DOI: 10.1016/j.clon.2012.04.001

22 Dreyfuss AD, Goia D, Shoniyozov K, Shewale SV, Velalopoulou A, Mazzoni S, Avgousti H, Metzler SD, Bravo PE, Feigenberg SJ, Ky B, Verginadis II and Koumenis C: A novel mouse model of radiation-induced cardiac injury reveals biological and radiological biomarkers of cardiac dysfunction with potential clinical relevance. Clin Cancer Res *27(8)*: 2266-2276, 2021. PMID: 33542079. DOI: 10.1158/1078-0432.CCR-20-3882

23 Nolan MT, Russell DJ and Marwick TH: Long-term risk of heart failure and myocardial dysfunction after thoracic radiotherapy: a systematic review. Can J Cardiol *32(7)*: 908-920, 2016. PMID: 27179544. DOI: 10.1016/j.cjca.2015.12.020

24 Sardaro A, Petruzzelli MF, D'Errico MP, Grimaldi L, Pili G and Portaluri M: Radiation-induced cardiac damage in early left breast cancer patients: risk factors, biological mechanisms, radiobiology, and dosimetric constraints. Radiother Oncol *103(2)*: 133-142, 2012. PMID: 22391054. DOI: 10.1016/j.radonc.2012.02.008

25 Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C and Hall P: Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med *368(11)*: 987-998, 2013. PMID: 23484825. DOI: 10.1056/NEJMoa1209825

26 Angermann CE, Nassau K, Stempfle HU, Krüger TM, Drewello R, Junge R, Uberfuhr P, Weiss M and Theisen K: Recognition of acute cardiac allograft rejection from serial integrated backscatter analyses in human orthotopic heart transplant recipients. Comparison with

conventional echocardiography. Circulation *95(1)*: 140-150, 1997. PMID: 8994429. DOI: 10.1161/01.cir.95.1.140

27 Duygu H, Akman L, Ozerkan F, Akercan F, Zoghi M, Nalbantgil S, Erturk U, Akilli A, Onder R and Akin M: Comparison of the effects of new and conventional hormone replacement therapies on left ventricular diastolic function in healthy postmenopausal women: a Doppler and ultrasonic backscatter study. Int J Cardiovasc Imaging *25(4)*: 387-396, 2009. PMID: 19194783. DOI: 10.1007/s10554-009-9429-2

28 Jin X, Rong S, Mei C, Ye C, Chen J and Chen X: Effects of thrice-weekly in-center nocturnal *vs*. conventional hemodialysis on integrated backscatter of myocardial tissue. Hemodial Int *15(2)*: 200-210, 2011. PMID: 21395972. DOI: 10.1111/j.1542-4758.2011.00537.x

29 Sritharan HP, Delaney GP, Lo Q, Batumalai V, Xuan W and Thomas L: Evaluation of traditional and novel echocardiographic methods of cardiac diastolic dysfunction post radiotherapy in breast cancer. Int J Cardiol *243*: 204-208, 2017. PMID: 28587740. DOI: 10.1016/j.ijcard.2017.05.007

30 Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, Ruddy KJ, Yan E and Redfield MM: Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation *135(15)*: 1388-1396, 2017. PMID: 28132957. DOI: 10.1161/CIRCULATIONAHA.116.025434

31 Trivedi SJ, Choudhary P, Lo Q, Sritharan HP, Iyer A, Batumalai V, Delaney GP and Thomas L: Persistent reduction in global longitudinal strain in the longer term after radiation therapy in patients with breast cancer. Radiother Oncol *132*: 148-154, 2019. PMID: 30414755. DOI: 10.1016/j.radonc.2018.10.023

32 Chen L, Ta S, Wu W, Wang C and Zhang Q: Prognostic and added value of echocardiographic strain for prediction of adverse outcomes in patients with locally advanced non-small cell lung cancer after radiotherapy. Ultrasound Med Biol *45(1)*: 98-107, 2019. PMID: 30366608. DOI: 10.1016/j.ultrasmedbio.2018.09.012

33 Li J, Wang L, Liu H, Zhang Z, Dong S, Zhang Y, Wu X, Wang C, Ji X, Ma H and Ren C: Analysis of the value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and other parameters related to right heart function in detecting acute radiation-induced right heart injury. Ann Palliat Med *10(6)*: 6455-6466, 2021. PMID: 34154350. DOI: 10.21037/apm-21-1014

Received January 21, 2022
Revised March 6, 2022
Accepted March 18, 2022