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Clinical Investigation

Cardiac Function After Radiation Therapy for Breast Cancer

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Summary

The relationship between individual cardiac dose distributions and systolic and diastolic dysfunction is unclear. We conducted a cross-sectional study consisting of 109 breast cancer survivors treated with postoperative radiation therapy (RT). The

Purpose: The main purpose of this study was to test the hypothesis that incidental cardiac irradiation is associated with changes in cardiac function in breast cancer (BC) survivors treated with radiation therapy (RT).

Methods and Materials: We conducted a cross-sectional study consisting of 109 BC survivors treated with RT between 2005 and 2011. The endpoint was cardiac function, assessed by echocardiography. Systolic function was assessed with the left ventricular ejection fraction (LVEF) (n = 107) and the global longitudinal strain (GLS) of the left ventricle (LV) (n = 52). LV diastolic dysfunction (n = 109) was defined by e' at the lateral and septal region, which represents the relaxation velocity of the myocardium. The individual calculated RT dose parameters of the LV and coronary arteries were collected from 3-dimensional

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endpoint was systolic and diastolic cardiac function, assessed by echocardiography. Although no relation between RT dose parameters and left ventricle ejection fraction was found, an association between individual RT dose and global longitudinal systolic strain of the left ventricle was determined.

computed tomography–based planning data. Univariable and multivariable analysis using forward selection was performed to identify the best predictors of cardiac function. Robustness of selection was assessed using bootstrapping. The resulting multivariable linear regression model was presented for the endpoints of systolic and diastolic function.

Results: The median time between BC diagnosis and echocardiography was 7 years. No relation between RT dose parameters and LVEF was found. In the multivariable analysis for the endpoint GLS of the LV, the maximum dose to the left main coronary artery was most often selected across bootstrap samples. For decreased diastolic function, the most often selected model across bootstrap samples included age at time of BC diagnosis and hypertension at baseline. Cardiac dose-volume histogram parameters were less frequently selected for this endpoint.

Conclusions: This study shows an association between individual cardiac dose distributions and GLS of the LV after RT for BC. No relation between RT dose parameters and LVEF was found. Diastolic function was most associated with age and hypertension at time of BC diagnosis. Further research is needed to make definitive conclusions.

Introduction

Adjuvant radiation therapy (RT) for breast cancer (BC) has been associated with a wide variety of cardiac diseases.[1] In relation to BC radiation, risk of ischemic heart disease has been well established.[2-4] Recent studies have shown significant relationships between RT to the whole heart and left ventricle (LV) and acute coronary events in BC populations.[5,6] However, the relationship between thoracic RT and cardiac dysfunction is less clear.

The left ventricular ejection fraction (LVEF) by echocardiography is the cornerstone of LV systolic function assessment in clinical practice. However, LVEF can underestimate actual cardiac damage because of the compensatory reserve of the myocardium that enables adequate ventricular outcome even in the presence of dysfunctional myocytes.[7] Global longitudinal systolic strain (GLS) is an echocardiographic technique that detects and quantifies subclinical and subtle disturbances in LV systolic function and can thus be considered as an early marker for radiation-induced cardiac damage.[8] This is particularly relevant because the latency time for symptomatic radiation-induced cardiovascular diseases is relatively long. These early markers may be helpful to identify patients at risk for major cardiac events who may benefit from preventive strategies.

The aim of this study was to assess the relationship between radiation dose to the LV and radiation dose to the coronary arteries and LV systolic and diastolic function in BC survivors treated with RT based on individual planned 3-dimensional (3D) dose distributions and computed tomography (CT) information.

Methods and Materials

Study population

The Department of General Practice of the University Medical Center Groningen (UMCG) performed a cross-sectional, population-based study to assess the frequency of cardiac dysfunction in female BC survivors in a primary care setting.[9] Patients were included if they received a diagnosis of BC stage I to III and had no disease activity for at least 5 years after treatment. Information could be extracted from electronic patient records of 1 of 80 participating primary care physicians (PCPs) in the northern Netherlands region. Patients were excluded if they had metastatic disease at the time of BC diagnosis, had a history of other malignancies, or received prior chemotherapy or RT treatment of other malignancies. The main study included 350 BC survivors treated from 1988 to 2011. All 350 patients underwent echocardiography. Because of the inclusion criteria of the main study with the date of treatment mostly in the pre-CT era, patients were only selected when CT-based RT treatment planning data were available. Therefore, our total study population was composed of 109 BC survivors treated with RT from 2005 to 2011.

All patients were treated with breast-conserving surgery followed by adjuvant RT. Patients with node-positive disease and patients who were high risk and node negative were treated with adjuvant systemic treatment including endocrine therapy, according to the national guidelines.

Data collection

Citizens of the Netherlands are registered in an electronic record of a PCP. The PCP captures all information

according to the International Classification of Primary Care.[10] Relevant data were collected using the International Classification of Primary Care codes for cardiovascular risk factors (dyslipidemia, hypertension, and diabetes mellitus) and cardiovascular disease (heart failure, ischemic heart disease, acute myocardial infarction, coronary artery sclerosis, atrial fibrillation, [supra]ventricular tachycardia, and nonrheumatic valve disease).

Detailed information about patient characteristics, tumor characteristics, systemic BC therapy (including chemotherapy, endocrine therapy, or Trastuzumab), and follow-up data were retrieved from hospital charts. The baseline date was defined as the date of BC diagnosis. The censoring date was defined as the date of the echocardiographic assessment. The medical ethics committee of the UMCG approved the study, which was registered at ClinicalTrials.gov (ID:NCT01904331).[9]

Radiation dosimetry

All 109 patients were treated with 3D conformal RT using CT-based treatment planning.[11] At the time of inclusion, cardiac sparing using breath-holding techniques was not yet implemented. Therefore, none of the patients were treated with a breath-hold technique. The reported doses are therefore higher than the typical cardiac exposure with modern planning and cardioprotective techniques.[12] The prescribed dose was 50.4 Gy delivered in 28 fractions to the whole breast with a simultaneous integrated boost of 14.0 or 16.8 Gy to a boost volume in the same 28 fractions, depending on pathological risk factors.

To analyze the relationship between cardiac function of the LV and incidental cardiac irradiation, contouring was performed of the LV and coronary arteries, responsible for the oxygenation of the LV. The LV was contoured using a multiatlas automatic segmentation tool based on the delineations by Feng et al (Mirada RTx [version 1.6]; Mirada Medical, Oxford, UK).[13] The contouring of the coronary arteries, including the left main coronary artery (LMCA), left anterior descending coronary artery, circumflex coronary artery (CX), and right coronary artery, was based on a recently published cardiac contouring guideline by Duane et al[14] and was done manually by 1 observer (example of a 3D reconstruction is shown in Fig. 1). After cardiac substructure delineation, the individual radiation dose to these substructures was recalculated using the original treatment plan. As a final step for this study, dose-volume histogram (DVH) parameters of the cardiac substructures were extracted from the treatment planning system (Pinnacle [version 9.1]; Philips Radiation Oncology, Fitchburg, WI).

Echocardiography parameters

As described previously, cardiac (dys)function was evaluated using echocardiography.[9] In short, all image acquisition and analysis was performed by a central reading lab

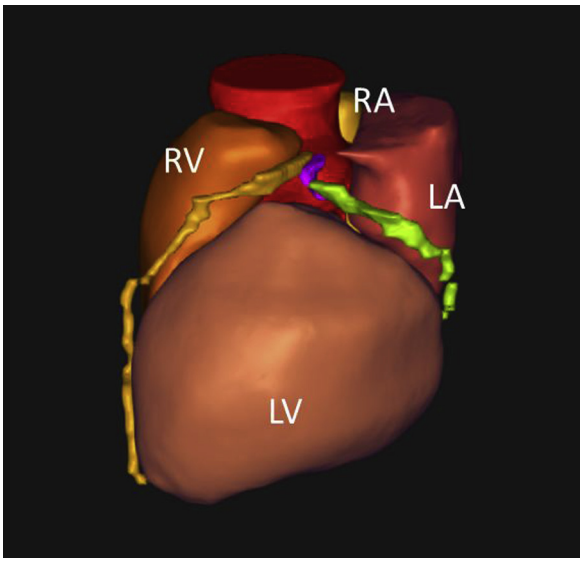

Fig. 1. Example of the contouring of the coronary arteries. The LV was contoured using a multiatlas automatic segmentation tool based on the delineations by Feng et al.[13] The contouring of the coronary arteries, including the left main coronary artery (purple), left anterior descending coronary artery (orange), and circumflex coronary artery (green) and right coronary artery (not shown in this figure) was done manually. *Abbreviations:* LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

(Groningen Imaging Core Laboratory) with Vivid E9 ultrasound equipment (GE, Horten, Norway), based on a predefined imaging and measurement protocol. All measurements were performed in accordance with the guidelines of the European Association of Cardiovascular Imaging/American Society of Echocardiography (ASE).[15]

Systolic function was evaluated in 2 ways, first by the LVEF, which was measured by the biplane method of disks summation (modified Simpson's rule). In cases where the image quality was too low to reliably determine the endocardial border, an estimation of LVEF was given by an experienced ultrasound technician. The LVEF was analyzed for 107 patients. Abnormal LVEF was defined as an LVEF $<54\%$, according to the European Association of Cardiovascular Imaging/ASE guidelines.[15] Additionally, GLS was determined as another measure of systolic function. For this reason, the echocardiograms were retrospectively analyzed for the GLS of the LV, using automated 2-dimensional speckle-tracking with TomTec Imaging Systems GmbH Arena 2 (Munich, Germany). For this analysis, we excluded all echocardiographies that were evaluated using eyeballing (n = 38), because the image quality was too low for a reliable assessment of this endpoint.

The remaining 71 echocardiographies were measured using Simpson's biplane method. Of those, 19 were excluded because of persistent inadequate tracking of GLS segments or incorrect tracing of the apex. Furthermore, the echocardiographies were checked for reproducibility of

GLS by analyzing inter- and intraobserver variability. The interclass correlation coefficient (ICC) was determined and accepted if greater than 0.6.[16,17] As a result, the GLS of the LV was retrospectively analyzed for 52 patients (flowchart in Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2019.02.003).

LV diastolic dysfunction was analyzed for 109 patients and defined by e' at the lateral and septal region, where e' represents the relaxation velocity of the myocardium in early diastole. Diastolic dysfunction was defined as e' lateral or e' septal at 2.5% below the normal range for each age group, according to the European Association of Echocardiography/ASE.[18] By calculating the average of e' septal and e' lateral together, a continuous variable was created.[19]

Statistical analysis

Patient characteristics (including cardiovascular risk factors [diabetes mellitus, hypertension, dyslipidemia, smoking, and body mass index], cardiac diseases [heart failure, arrhythmias, non-rheumatic valve disorder, and ischemic heart disease]), tumor characteristics and information about BC systemic treatment (chemotherapy, endocrine therapy and/or trastuzumab) and RT were described at the time of diagnosis and if applicable at the time of echocardiography using descriptive statistics. Clinical factors at time of diagnosis were included in the analysis because preexisting cardiac conditions in combination with RT were found to increase the risk of subsequent cardiac events.[5,6] Arrhythmias included supraventricular tachycardia, ventricular paroxysmal tachycardia, and/or atrial fibrillation. Nonrheumatic valve disorder included aortic stenosis and/or mitral valve insufficiency. Ischemic heart diseases included coronary atherosclerosis, myocardial infarction, and/or angina pectoris. Using DVH data from each patient's RT plan, we first calculated the mean dose, maximum dose, and mean V(x) in bins of 5 Gy, where V(x) refers to the relative volume (in percentage) of the cardiac substructures that received a dose of x Gy. Both systolic and diastolic function were defined as binary variables and as continuous variables, whenever appropriate.

The first step in identifying associations between patient characteristics, risk factors, and treatment characteristics and the endpoints of systolic and diastolic function was a preselection based on intervariable correlation to reduce the number of variables. If the Pearson correlation of 2 variables was larger than 0.80, the variable with the strongest univariable association with the endpoint was selected.[20] Second, univariable and multivariable stepwise forward selection was used to select the most important risk factors. The entire variable selection procedure (preselection and forward selection) was repeated on 1000 bootstrapped samples of a size equal to the original study population and drawn with replacement. The resulting most frequently selected multivariable linear regression model was presented. This analysis was done for the endpoints LVEF, GLS of the LV, and diastolic function, respectively. Data were analyzed using MATLAB (version R2017a) and SPSS (IBM SPSS Statistics, version 22, IBM Corp).

Results

Patient characteristics

The characteristics of the patients at baseline and at the time of echocardiography are summarized in Table 1. Tumor and treatment characteristics are summarized in Table 2. The median age at diagnosis was 55 years (interquartile range [IQR], 49-60), and the median age at time of echocardiography was 62 years (IQR, 56-67). The median follow-up time was 7 years (IQR, 5-8).

Results of echocardiography

Systolic function

The results of echocardiography are summarized in Table 3. Using LVEF <54% as a cutoff value, 15 of 107 BC survivors (14%) had an abnormal LVEF at the time of echocardiography.

We further analyzed the data by investigating a possible relationship between radiation dose and posttreatment LVEF. Clinical factors (age, diabetes mellitus, hypertension, dyslipidemia, smoking, and number of pack-years), systemic therapy (chemotherapy, endocrine therapy, and trastuzumab), and DVH parameters (mean dose, maximum dose, and mean V[x] in bins of 5 Gy) of the LV and coronary arteries were entered in the multivariable analysis before application of forward selection. Results of the variable selection in the 1000 bootstrap samples are shown in Figures E2 and E3 (available online at https://doi.org/10.1016/j.ijrobp.2019.02.003). No relationships with RT dose parameters or use of systemic therapy were found. In the final model, LVEF was associated with smoking at time of diagnosis (Table E1; available online at https://doi.org/10.1016/j.ijrobp.2019.02.003).

Because a decreased LVEF indicates relatively late and severe cardiac damage, we performed an additional analysis using the subclinical parameter GLS of the LV as an endpoint. According to 52 echocardiographies, the mean GLS of the LV was −16.95% (range, −23.26% to −9.44%). The multivariable analysis included the following risk factors before variable selection: clinical factors (age, diabetes mellitus, hypertension, dyslipidemia, smoking, and number of pack-years), systemic therapy variables (chemotherapy, endocrine therapy, and trastuzumab), and DVH parameters (mean dose, maximum dose, and mean V[x] in bins of 5 Gy) of the LV and coronary arteries. On the basis of variable selection in the 1000 bootstrap samples, we found that the maximum dose to the LMCA was selected

Table 1 Patient characteristics at the time of breast cancer diagnosis and at the time of echocardiography for all 109 breast cancer survivors

BC population (N = 109)		
Variable	At baseline	At time of echocardiography
Age at BC diagnosis, y		
Median	55	62
IQR	49-60	56-67
Follow-up interval, y		
Median	-	7
IQR	-	5-8
Cardiovascular risk factors		
Diabetes mellitus, n (%)		
Yes	6 (5.5)	10 (9.2)
No	103 (94.5)	99 (90.8)
Hypertension, n (%)		
Yes	18 (16.5)	35 (32.1)
No	91 (83.5)	74 (67.9)
Dyslipidemia, n (%)		
Yes	6 (5.5)	20 (18.3)
No	103 (94.5)	89 (81.7)
Smoking, n (%)		
Yes	30 (27.5)	24 (22.0)
No	79 (72.5)	85 (78.0)
No. of pack-years		
Median	14.48	16.75
Range	1.43-41.16	0.60-55.00
Cardiac diseases*		
Complaints of heart failure, n (%)		
Yes	0 (0.0)	0 (0.0)
No	109 (100.0)	109 (100.0)
Arrhythmias, n (%)†		
Yes	0 (0.0)	8 (7.3)
No	109 (100.0)	101 (92.7)
Nonrheumatic valve disorder, n (%)‡		
Yes	0 (0.0)	0 (0.0)
No	109 (100.0)	109 (100.0)
Ischemic heart diseases, n (%)§		
Yes	1 (0.9)	3 (2.8)
No	108 (99.1)	106 (97.2)

Abbreviations: BC = breast cancer; BMI = body mass index; IQR = interquartile range.

* As reported by their primary care physician or stated in their hospital medical charts.

† Arrhythmias included supraventricular paroxysmal tachycardia, ventricular paroxysmal tachycardia, and/or atrial fibrillation.

‡ Nonrheumatic valve disorder included aortic stenosis and/or mitral valve insufficiency.

§ Ischemic heart diseases included coronary atherosclerosis, myocardial infarction, and unstable/stable angina pectoris.

most across bootstrap samples (Fig. E4; available online at https://doi.org/10.1016/j.ijrobp.2019.02.003). All DVH parameters that were selected related to dose to the coronary arteries, not to the LV. The frequency plot of the selected models is shown in Figure E5 (available online at https://doi.org/10.1016/j.ijrobp.2019.02.003). Model characteristics of the final model for the endpoint GLS of the LV, consisting of the maximum dose to the LMCA, are shown in Table 4.

Diastolic function

Using e' lateral or e' septal at 2.5% below the normal range for each age group as a cutoff value, 43 of 109 (39%) BC survivors had diastolic dysfunction (Table 2).

The multivariable analysis included the same risk factors before variable selection: clinical factors (age, diabetes mellitus, hypertension, dyslipidemia, smoking, and number of pack-years), systemic therapy variables (chemotherapy, endocrine therapy, and trastuzumab), and DVH parameters (mean dose, maximum dose, and mean V[x] in bins of 5 Gy) of the LV and coronary arteries. On the basis of variable selection in the 1000 bootstrap samples, we found that clinical variables were selected most across bootstrap samples (Fig. E6; available online at https://doi.org/10.1016/j.ijrobp.2019.02.003). Variable age at baseline was selected 1000 times from 1000 bootstrap samples, and hypertension at baseline was selected 629 times. DVH parameters were less frequently selected for this endpoint. The frequency plot of the selected models is shown in Figure E7 (available online at https://doi.org/10.1016/j.ijrobp.2019.02.003). Details of the final model for the endpoint diastolic function, consisting of age at baseline and hypertension, are shown in Table 5.

Discussion

This study shows an association between individual cardiac dose distributions and subclinical systolic dysfunction of the LV after RT for BC. The subclinical marker, GLS of the LV, was most associated with the maximum dose to the LMCA. Notably, all DVH parameters that were selected for this endpoint were based on dose to the coronary arteries. The final model for diastolic function included age and hypertension at baseline. DVH parameters were less frequently selected for this endpoint.

Previous studies have shown similar results with regard to systolic function using LVEF as a primary endpoint.[21-23] In these studies, with a median follow-up time of 6 to 13 years, no significant decrease in LVEF after RT treatment for BC was observed.[21-23] Additionally, in a recently published meta-analysis, RT was found to be associated with an increased risk of coronary heart disease, but not with a significant decline in LVEF.[4] In the current study based on 3D cardiac dose distributions, no relation between RT dose and decline in LVEF was found either. Changes in LVEF reflect severe damage that may manifest relatively late because of compensation mechanisms.[24] Given the median follow-up time of 7 years in the current study, the interval may be too short for the development of a decreased LVEF of <54%. Because of the limitations in sensitivity and reproducibility

Table 2 Tumor and treatment characteristics at the time of breast cancer diagnosis for all 109 breast cancer survivors

Variable	At baseline
Tumor characteristics, n (%)	
Laterality BC	
Left (-sided BC)	56 (51.4)
Right (-sided BC)	53 (48.6)
Size (T stage)	
T0	2 (1.8)
T1	77 (70.6)
T2	16 (14.7)
T3	2 (1.8)
Unknown	12 (11.0)
Nodes (N stage)	
N0	66 (60.6)
N1	22 (20.2)
N2	6 (5.5)
N3	3 (2.8)
Unknown	12 (11.0)
Radiation therapy, median (range) (Gy)	
Mean heart dose	
Total	2.24 (0.61-11.34)
Right breast	1.29 (0.61-4.14)
Left breast	4.29 (1.07-11.34)
LV dose	
Total	1.49 (0.23-18.85)
Right breast	0.61 (0.23-1.62)
Left breast	6.15 (0.72-18.85)
LMCA dose	
Total	1.42 (0.23-6.35)
Right breast	0.88 (0.23-3.08)
Left breast	2.29 (0.70-6.35)
LAD dose	
Total	1.73 (0.23-40.94)
Right breast	0.90 (0.23-1.73)
Left breast	20.57 (1.25-40.94)
CX dose	
Total	1.38 (0.13-6.72)
Right breast	0.56 (0.13-2.66)
Left breast	1.90 (0.66-6.72)
RCA dose	
Total	1.61 (0.46-7.05)
Right breast	1.68 (0.74-7.05)
Left breast	1.57 (0.46-2.72)
Additional systemic therapy, n (%)	
Chemotherapy only	
Yes	15 (13.8)
No	94 (86.2)
Endocrine therapy only	
Yes	12 (11.0)
No	97 (89.0)
Combination chemotherapy and endocrine therapy	
Yes	27 (24.8)
No	82 (75.2)
Trastuzumab	
Yes	6 (5.5)
No	103 (94.5)

Abbreviations: BC = breast cancer; CX = circumflex coronary artery; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; LV = left ventricle; N = nodes; RCA = right coronary artery; T = tumor.

of the LVEF, we decided to also use the GLS of the LV, which is a more sensitive method to detect subclinical systolic dysfunction of the LV.[25]

Two studies looked at both LVEF and GLS in BC survivors.[26,27] They found no significant decrease in LVEF after RT in patients with either left- or right-sided BC between 2 and 14 months of follow-up. However, a significant decrease in longitudinal strain immediately after RT and at 8 and 14 months after RT was found for left-sided BC survivors, but not for right-sided BC survivors, suggesting a dose-effect relationship. Another study found that patients with left-sided BC experienced a decline in apical and global strain values, whereas patients with right-sided BC showed a decline in the basal anterior segment of the LV. Furthermore, RT caused no changes in conventional LV systolic measurements.[28] However, the researchers did not examine any associations between cardiac dose parameters and GLS of the LV. In line with the current study, these results indicate that GLS is a more sensitive measure for cardiac changes after BC RT and that these changes are already present relatively early after completion of RT.

Several studies suggest that GLS provides independent prognostic information regarding cardiovascular morbidity and mortality in the general population.[29-31] Presence of worse LV strain at baseline was associated with a higher risk for incident heart failure and all-cause mortality over the follow-up period.[31] This issue is particularly important in BC populations because it may take years for clinically overt cardiac damage to develop. The detection of early changes could be predictive for late RT-induced cardiac morbidity.[26]

Knowledge of the exact underlying mechanism behind radiation-induced cardiac toxicity is lacking. In particular, it is not clear whether coronary artery damage or myocardial damage, or both, are responsible for radiation-induced heart disease.[32] Our results suggest that RT to the coronary arteries is associated with subclinical systolic dysfunction. As shown in Table 4, the most selected risk factor of posttreatment GLS is the maximum dose to the LMCA. This result was also supported by the frequency tables in the Supplemental Material (available online at https://doi.org/10.1016/j.ijrobp.2019.02.003); DVH parameters of the coronary arteries were strongly dominant relative to DVH parameters of the myocardium. Previous research has shown a direct link between radiation dose and the location of coronary stenosis, mostly in the left anterior descending coronary artery.[33,34] These studies support the importance

Table 3 Results of echocardiography after a median follow-up time of 7 years

Variable	At time of echocardiography	%
Left ventricular ejection fraction (%) based on 107 patients with BC*		
Mean	58.04	
Range	41.00-71.00	
Missing	2	1.8
Abnormal left ventricular ejection fraction†		
Yes	15	13.8
No	92	84.4
Missing	2	1.8
Left ventricle global longitudinal strain (%) based on 52 patients with BC‡		
Mean	−16.95	
Range	−23.26 to −9.44	
Missing because of limited quality	57	52.3
Left ventricle diastolic function (cm/s) based on 109 patients with BC§		
Mean	9.00	
Range	3.45-16.05	
Missing	0	0.0
Abnormal left ventricle diastolic function‖		
Yes	43	39.4
No	66	60.6
Missing	0	0.0

Abbreviation: BC = breast cancer.

* Measured left ventricular ejection fraction with biplane method of disks summation (modified Simpson's rule), if not available with eyeballing.

† Defined as a left ventricular ejection fraction <54% according to the European Association of Cardiovascular Imaging/American Society of Echocardiography.

‡ Measured using automated 2-dimensional speckle-tracking.

§ Average of the mean e' septal and e' lateral.

‖ Defined as e' lateral or e' septal 2.5% below the normal range for each age group, according to the European Association of Echocardiography/American Society of Echocardiography. In this cohort, the mean e' septal was 7.79 (range, 3.00-14.40), and the mean e' lateral was 10.28 (range, 3.90-18.60).

Table 4 Model characteristics of the final model for the endpoint global longitudinal systolic strain of the left ventricle in breast cancer survivors within first 10 years after radiation therapy

Variable	B	SE	95% CI for B	*P* value*
D_{max} LMCA	0.883	0.342	0.195-1.570	.013

Abbreviations: B = regression coefficient; CI = confidence interval; D_{max} = maximum dose; LMCA = left main coronary artery; SE = standard error.

Results are based on 52 breast cancer survivors.

* *P* value between the variable and the endpoint global longitudinal strain of the left ventricle, calculated using linear regression analysis.

of the coronary arteries in the pathogenesis of radiation-induced cardiac toxicity.

It could be hypothesized that irradiation of coronary arteries may initiate inflammation, coronary spasms, or rupture of an existing atherosclerotic plaque, resulting in insufficient supply of oxygenated blood to the myocardium. This can eventually lead to secondary damage to the myocardium, in addition to direct radiation-induced local damage to the microvascular endothelial cells, leading to microvascular rarefaction and myocardial inflammation, oxidative stress, and fibrosis.[35,36] However, the exact mechanisms of radiation-associated cardiac damage remain to be determined.

We found an association between clinical variables and diastolic function. Our results showed that age and hypertension at time of BC diagnosis were selected most for the endpoint diastolic function in the 1000 bootstrap samples. This outcome is consistent with previous studies, which have also shown no significant increased risk of LV diastolic dysfunction after BC treatment.[9,23,37]

A limitation of our study is its cross-sectional design. We did not have echocardiography data before RT, and therefore we are not able to report on possible changes after RT. However, the relationship found for systolic (GLS) function suggests that RT might play a role in the etiology of these effects. The decline in cardiac function in relation to the dose of radiation is subtle. This subtlety makes it difficult to identify differences between patient groups and control groups. By using dose-effect relationships, we are able to identify small changes that cannot be found just by comparing irradiated and nonirradiated populations.

It was also possible to consider patient age and follow-up time, although in our analysis age was not associated with the decline in systolic cardiac function but was associated with a decline in diastolic function. Follow-up time was not associated with systolic or diastolic function. Moreover, it is important to note that we performed explorative analysis in this study. Therefore, prospective data still need to be collected within studies such as the BACCARAT prospective cohort study or the MEDIRAD EARLY HEART study.[8,38] The results of the current study should therefore be considered as hypothesis generating, not for making definitive conclusions. Further research and validation in other and larger cohorts is needed to confirm our results.

Another limitation is that it remains to be determined if, in this specific group of patients, subclinical effects will eventually translate into major cardiac events. However, as shown in the general population, GLS provides independent and additional prognostic information regarding long-term risk of cardiovascular morbidity and mortality.[29]

Table 5 Model characteristics of the final model for the endpoint diastolic function of the left ventricle in breast cancer survivors within first 10 years after radiation therapy

Variable	B	SE	95% CI for B	*P* value*
Age at BC diagnosis	−0.155	0.021	−0.197 to −0.133	.000
Hypertension	−1.309	0.536	−2.372 to −0.246	.016

Abbreviations: B = regression coefficient; BC = breast cancer; CI = confidence interval; SE = standard error.
Results are based on 109 breast cancer survivors.
* *P* value between the variable and the endpoint diastolic function of the left ventricle, calculated using linear regression analysis.

Conclusions

This study shows an association between individual RT dose for BC and GLS of the LV. Our results suggest that these adverse effects are associated with radiation dose to the coronary arteries. Diastolic function was associated with age and hypertension at time of BC diagnosis; DVH parameters were less frequently selected for this endpoint.

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