Cardiac Function After Radiation Therapy for Breast Cancer

van den Bogaard, Veerle A. B.; van Luijk, Peter; Hummel, Yoran M.; van der Meer, Peter; Schuit, Ewoud; Boerman, Liselotte M.; Maas, Saskia W. M. C.; Nauta, Jan F.; Steggink, Lars C.; Gietema, Jourik A.

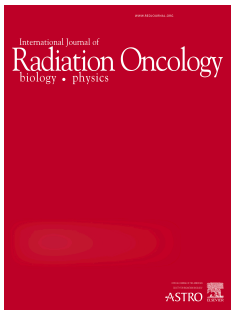
Published in:
International Journal of Radiation Oncology, Biology, Physics

DOI:
10.1016/j.ijrobp.2019.02.003

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2019

Accepted Manuscript



Cardiac Function After Radiotherapy for Breast Cancer

Veerle A.B. van den Bogaard, MD, Peter van Luijk, PhD, Yoran M. Hummel, PhD, Peter van der Meer, MD, PhD, E. Schuit, PhD, Liselotte M. Boerman, MD, Saskia W.M.C. Maass, MD, Jan.F. Nauta, MD, Lars C. Steggink, MD, Jourik A. Gietema, MD, PhD, Geertruida H. de Bock, PhD, Annette J. Berendsen, MD, PhD, Wilma G.J.M. Smit, MD, Nanna M. Sijtsema, PhD, Roel G.J. Kierkels, MSc, Johannes A. Langendijk, MD, PhD, Anne P.G. Crijns, MD, PhD, John H. Maduro, MD, PhD

PII: S0360-3016(19)30193-2

DOI: https://doi.org/10.1016/j.ijrobp.2019.02.003

Reference: ROB 25528

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 8 August 2018

Revised Date: 25 January 2019

Accepted Date: 4 February 2019

Please cite this article as: van den Bogaard VAB, van Luijk P, Hummel YM, van der Meer P, Schuit E, Boerman LM, Maass SWMC, Nauta JF, Steggink LC, Gietema JA, de Bock GH, Berendsen AJ, Smit WGJM, Sijtsema NM, Kierkels RGJ, Langendijk JA, Crijns APG, Maduro JH, Cardiac Function After Radiotherapy for Breast Cancer, *International Journal of Radiation Oncology • Biology • Physics* (2019), doi: https://doi.org/10.1016/j.ijrobp.2019.02.003.

Cardiac Function After Radiotherapy for Breast Cancer

Names of each author's institution and an indication of each author's affiliation:

Veerle A.B. van den Bogaard, MD[1]; Peter van Luijk, PhD[1]; Yoran M. Hummel, PhD[2]; Peter van der Meer, MD, PhD[2]; E. Schuit, PhD[3]; Liselotte M. Boerman, MD[4]; Saskia W.M.C. Maass, MD[4]; Jan. F. Nauta, MD[2]; Lars C. Steggink, MD[5]; Jourik A. Gietema, MD, PhD[5]; Geertruida H. de Bock, PhD[6]; Annette J. Berendsen, MD, PhD[4]; Wilma G.J.M. Smit, MD[7]; Nanna M. Sijtsema, PhD[1]; Roel G.J. Kierkels, MSc[1]; Johannes A. Langendijk, MD, PhD[1]; Anne P.G. Crijns, MD, PhD[1] and John H. Maduro, MD, PhD[1]

[1] Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30, 001, 9700 RB Groningen, The Netherlands.

[2] Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30, 001, 9700 RB Groningen, The Netherlands.

[3] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands.

[4] Department of General Practice, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30, 001, 9700 RB Groningen, The Netherlands.

[5] Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30, 001, 9700 RB Groningen, The Netherlands.

[6] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30, 001, 9700 RB Groningen, The Netherlands.

[7] Department of Radiation Oncology, Radiotherapy Institute Friesland, Borniastraat 36, P.O. Box 30, 001, 8934 AD Leeuwarden, The Netherlands.

Author(s) responsible for statistical analyses:

Veerle A.B. van den Bogaard

Department of Radiation Oncology
University Medical Center Groningen
P.O. Box 30001, 9700 RB Groningen
The Netherlands
Telephone number: +31-50-3619440
Email address: v.a.b.van.den.bogaard@umcg.nl

Peter van Luijk

Department of Radiation Oncology
University Medical Center Groningen
P.O. Box 30001, 9700 RB Groningen
The Netherlands
Telephone number: +31-50-3611739
Email address: p.van.luijk@umcg.nl

Ewoud Schuit

Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
Universiteitsweg 100, 3584 CG Utrecht
The Netherlands
Email: E.Schuit@umcutrecht.nl

Geertruida H. de Bock

Department of Epidemiology
University Medical Center Groningen
P.O. Box 30001, 9700 RB Groningen
The Netherlands
Telephone number: +31-50-3610938
Email address: g.h.de.bock@umcg.nl

Johannes A. Langendijk

Department of Radiation Oncology
University Medical Center Groningen
P.O. Box 30001, 9700 RB Groningen
The Netherlands
Telephone number: +31-50-3613708
Email address: j.a.langendijk@umcg.nl

Corresponding author:
John H. Maduro, MD, PhD
Department of Radiation Oncology
University Medical Center Groningen
P.O. Box 30001, 9700 RB Groningen
The Netherlands
Fax number: +31-50-3613672
Telephone number: +31-50-3649375
Email address: j.h.maduro@umcg.nl

Short running title: Cardiac Function after Breast Irradiation

Acknowledgments: not applicable

Conflict of interest: Johannes A. Langendijk, MD, PhD reports a honorarium for consultancy paid to UMCG Research BV by IBA, research collaboration agreement with IBA, research collaboration agreement with Philips, research collaboration agreement with Mirada, R&D collaboration agreement with RaySearch, outside

the submitted work. There are no financial and personal relationships with other people or organizations that could inappropriately influence the other authors work.

ABSTRACT

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 radiotherapy (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 ventricle 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 three-dimensional CT-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 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 (DVH) 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 radiotherapy (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[2,3,4]. Recent studies have shown significant relationships between RT to the whole heart (WH) 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 early marker for radiation-induced cardiac damage[8]. This is particularly relevant, as 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 that 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 3D dose distributions and computed tomography (CT) information.

METHODS AND MATERIALS

Study Population

The Department of General Practice of XXXX 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 were diagnosed with BC stage I–III and had no disease activity for at least 5 years after treatment. Information could be extracted from electronic patient records of one 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 and/or received prior chemotherapy or RT treatment for other malignancies. The main study included 350 BC survivors treated from 1988 to 2011. All 350 patients underwent an echocardiography. Due to 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 was 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 high risk node negative patients 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 primary care physician (PCP). The PCP captures all information according to the International Classification of Primary Care (ICPC)[10]. Relevant data was collected using the ICPC 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 non-rheumatic valve disease).

Detailed information about patient characteristics, tumor characteristics, systemic BC therapy (including chemotherapy and/or endocrine therapy and/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 XXXX approved the study which was registered at clinicaltrials.gov [ID:XXXX][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 e.g. 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 multi-atlas automatic segmentation tool based on the delineations by Feng *et al.* (Mirada RTx [version 1.6]; Mirada Medical, Oxford, United Kingdom)[13]. The contouring of the coronary arteries, including the left main coronary artery (LMCA), left anterior descending coronary artery (LAD) and circumflex coronary artery (CX) and right coronary artery (RCA) was based on a recently published cardiac contouring guideline by Duane *et al.*[14] and was done manually by one observer (example of a 3D reconstruction is shown in figure 1). Following cardiac substructure delineation, the individual radiation dose to these substructures was re-calculated 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, Fitsburg, 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 (XXXX Imaging Core Laboratory) with VIVID E9 ultrasound equipment (GE, Horton, Norway), based on a predefined imaging and measurement protocol. All measurements were performed in accordance with the guidelines of the European Association for Cardio Vascular Imaging/American Society of Echocardiography (EACVI/ASE)[15].

Systolic function was evaluated in two ways. First by the left ventricular ejection fraction (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 EACVI/ASE guidelines[15]. Additionally, global longitudinal systolic strain (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 2D-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), as 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 due to persistent inadequate tracking of GLS segments, or due to incorrect tracing of the apex. Furthermore, the echocardiographies were checked for reproducibility of GLS by analyzing inter- and intra-observer variability. The interclass correlation coefficient (ICC) was determined and accepted if ICC was greater than 0.6[16,17]. As a result, the GLS of the LV was retrospectively analyzed for 52 patients (flow-chart figure 1 in the supplemental material).

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/American Society of Echocardiography (EAE/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 (BMI)), 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, as pre-existing 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. Non-rheumatic 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 was 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 systolic and diastolic function, was a pre-selection based on intervariable correlation to reduce the number of variables. If the Pearson correlation of two variables was larger than 0.80, the variable with the strongest univariable association with the endpoint was selected[20]. Secondly, univariable and multivariable stepwise forward selection was used to select the most important risk factors. The entire variable selection procedure (pre-selection and forward selection) was repeated on 1000 bootstrapped samples of equal size as the original study population and that were 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 was 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 Echocardiography

Systolic function

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

We further analyzed the data by investigating a possible relationship between radiation dose and post-treatment 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 supplementary material figures 2 and 3. 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 (supplementary material table 1).

As 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. Based on 52 echocardiographies, the mean GLS of the LV was -16.95% (range=-23.26%– -9.44%). Based on the multivariable analysis, that 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, we found that the maximum dose to the LMCA was selected most across bootstrap samples (supplementary material figure 4). 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 5 in the supplementary material. 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 cut-off value, 43 out of 109 (39%) BC survivors had a diastolic dysfunction (table 2).

Based on the multivariable analysis, that 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, we found that clinical variables were selected most across bootstrap samples (supplementary material figure 6). The variable age at baseline was selected 1000 times out of 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 7 in the supplementary material. 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. Notable, 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[21,22,23]. In these studies, with a median follow-up time of 6 to 13 years, no significant decrease in LVEF after RT treatment for BC has been observed[21,22,23]. 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. It should be noted that changes in LVEF reflect severe damage that may manifest itself relatively late, due to compensation mechanisms[24]. Given the median follow-up time in the current study of 7 years, the interval may be too short for the development of a decreased LVEF of <54%. Because of the limitations in sensitivity and reproducibility 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 two 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 treatment.

Several studies suggest that GLS provides independent prognostic information regarding cardiovascular morbidity and mortality in the general population[29,30,31]. Presence of worse LV strain at baseline, was associated with higher risk for incident heart failure and all-cause mortality over the follow-up period[31]. This is particularly important in BC populations, as 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 on 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 post-treatment GLS is the maximum dose to the LMCA. This was also supported by the frequency tables in the supplemental material, 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 LAD[33,34]. These studies support the importance of the coronary arteries in the pathogenesis of radiation-induced cardiac toxicity.

It could be hypothesized that radiation 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 still 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 is consistent with previous studies that 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 prior to 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 non-irradiated populations.

It was also possible to take into account patient age and follow-up time; although in our analysis age was not associated with the decline in systolic cardiac function, but it 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 needs 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, and 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].

In conclusion, 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.

REFERENCES

1. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac Complications of Thoracic Irradiation. J Am Coll Cardiol. 2013;61:2319-2328. doi: 10.1016/j.jacc.2013.01.090.

2. McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, Fornander T, Gigante B, Jensen MB, Peto R, Rahimi K, Taylor CW, Ewertz M. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol. 2011;100:167-175. doi: 10.1016/j.radonc.2011.06.016.

3. Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, Solin LJ. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol. 2006;24:4100-4106. doi: 10.1200/JCO.2005.05.1037.

4. Cheng YJ, Nie XY, Ji CC, Lin XX, Liu LJ, Chen XM, Yao H, Wu SH. Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer. J Am Heart Assoc. 2017;6:e005633. doi: 10.1161/JAHA.117.005633.

5. 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, Hall P. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. N Engl J Med. 2013;368:987-998. doi: 10.1056/NEJMoa1209825.

6. XXXX

7. Altena R, Perik PJ, Van Veldhuisen DJ, De Vries EGE, Gietema JA. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. Lancet Oncol. 2009;10:391-399. doi: 10.1016/S1470-2045(09)70042-7.

8. Jacob S, Pathak A, Franck D, Latorzeff I, Jimenez G, Fondard O, Lapeyre M, Colombier D, Bruguiere E, Lairez O, Fontenel B, Milliat F, Tamarat R, Broggio D, Derreumaux S, Ducassou M, Ferrières J, Laurier D, Benderitter M, Bernier MO. Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT prospective cohort study. Radiat Oncol. 2016;11:54. doi: 10.1186/s13014-016-0627-5.

9. XXXX

10. Soler JK, Okkes I, Wood M, Lamberts H. The coming of age of ICPC: celebrating the 21st birthday of the International Classification of Primary Care. Fam Pract. 2008;25:312-317. doi: 10.1093/fampra/cmn028.

11. XXXX

12. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. Int J Radiat Oncol Biol Phys. 2015;93:845-853. doi: 10.1016/j.ijrobp.2015.07.2292.

13. Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, Hayman JA, Jagsi R, Jolly S, Larouere J, Soriano J, Marsh R, Pierce LJ. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2011;79:10-18. doi: 10.1016/j.ijrobp.2009.10.058.

14. Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, Lorenzen EL, McArdle O, Mcgale P, Myerson S, Rahimi K, Vivekanandan S, Warren S, Taylor CW. A cardiac contouring atlas for radiotherapy. Radiother Oncol. 2017;122:416-422. doi: 10.1016/j.radonc.2017.01.008.

15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14. doi: 10.1016/j.echo.2014.10.003.

16. Cicchetti DV. Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instrument in Psychology. Psychological Assessment. 1994;6:284-290. doi: 10.1037/1040-3590.6.4.284.

17. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15:155-63. doi: 10.1016/j.jcm.2016.02.012.

18. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. J Am Soc Echocardiogr. 2009;22:107-133. doi: 10.1016/j.echo.2008.11.023.

19. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129-2200. doi: 10.1093/eurheartj/ehw128.

20. Van der Schaaf A, Xu CJ, van Luijk P, Van't Veld AA, Langendijk JA, Schilstra C. Multivariate modeling of complications with data driven variable selection: guarding against overfitting and effects of data set size. Radiother Oncol. 2012;105:115-21. doi: 10.1016/j.radonc.2011.12.006.

21. Magné N, Castadot P, Chargari C, Di Leo A, Philippson C, Van Houtte P. Special focus on cardiac toxicity of different sequences of adjuvant doxorubicin/docetaxel/CMF regimens combined with radiotherapy in breast cancer patients. Radiother Oncol. 2009;90:116-121. doi: 10.1016/j.radonc.2008.10.003.

22. Pistevou-Gompaki K, Hatzitolios A, Eleftheriadis N, Boultoukas E, Ntaios G, Andronikidis I, Tzitzikas I. Evaluation of cardiotoxicity five years after 2D planned, non-simulated, radiation therapy for left breast cancer. Ther Clin Risk Manag. 2008;4:1359-1362. doi: 10.2147/TCRM.S2751.

23. Gustavsson A, Bendahl PO, Cwikiel M, Eskilsson J, Thapper KL, Pahlm O. No serious late cardiac effects after adjuvant radiotherapy following mastectomy in premenopausal women with early breast cancer. Int J Radiat Oncol Biol Phys. 1999;43:745-754. doi: 10.1016/S0360-3016(98)00454-4.

24. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J. 2016;37:1642-1650. doi: 10.1093/eurheartj/ehv510.

25. King A, Thambyrajah J, Leng E, Stewart MJ. Global longitudinal strain: a useful everyday measurement? Echo Res Pract. 2016;3:85-93. doi: 10.1530/ERP-16-0022.

26. Erven K, Jurcut R, Weltens C, Giusca S, Ector J, Wildiers H, Van den Bogaert W, Voigt JU. Acute Radiation Effects on Cardiac Function Detected by Strain Rate Imaging in Breast Cancer Patients. Int J Radiat Oncol Biol Phys. 2011;79:1444-1451. doi: 10.1016/j.ijrobp.2010.01.004.

27. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, Voigt JU, Weltens C. Subclinical Cardiotoxicity Detected by Strain Rate Imaging up to 14 months After Breast Radiation Therapy. Int J Radiat Oncol Biol Phys. 2013;85:1172-1178. doi: 10.1016/j.ijrobp.2012.09.022.

28. Tuohinen SS, Skyttä T, Poutanen T, Huhtala H, Virtanen V, Kellokumpu-Lehtinen P-L, 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. 2017;33:463-472. doi: 10.1007/s10554-016-1021-y.

29. Biering-Sørensen T, Biering-Sørensen SR, Olsen FJ, Sengeløv M, Jørgensen PG, Mogelvang R, Shah AM, Jensen JS. Global Longitudinal Strain by Echocardiography Predicts Long-Term Risk of Cardiovascular Morbidity and Mortality in a Low-Risk General Population: The Copenhagen City Heart

Study. Circ Cardiovasc Imaging. 2017;10:e005521. doi: 10.1161/CIRCIMAGING.116.005521.

30. Russo C, Jin Z, Elkind MSV, Rundek T, Homma S, Sacco RL, Di Tullio MR. Prevalence and Prognostic Value of Subclinical Left Ventricular Systolic Dysfunction by Global Longitudinal Strain in a Community-Based Cohort HHS Public Access. Eur J Hear Fail. 2014;16:1301-1309. doi: 10.1002/ejhf.154.

31. Cheng S, McCabe EL, Larson MG, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Solomon SD, Benjamin EJ, Vasan RS. Distinct Aspects of Left Ventricular Mechanical Function Are Differentially Associated With Cardiovascular Outcomes and All-Cause Mortality in the Community. J Am Heart Assoc. 2015;4:e002071. doi: 10.1161/JAHA.115.002071.

32. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, Darby SC. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. Int J Radiat Oncol Biol Phys. 2008;72:501-7. doi: 10.1016/j.ijrobp.2007.12.058.

33. Correa CR, Litt HI, Hwang WT, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. J Clin Oncol. 2007;25:3031-3037. doi: 10.1200/JCO.2006.08.6595.

34. Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjögren I, Lagerqvist B, Blomqvist C. Distribution of coronary artery stenosis after radiation for breast cancer. J Clin Oncol. 2012;30:380-386. doi: 10.1200/JCO.2011.34.5900.

35. Zagar TM, Cardinale DM, Marks LB. Breast cancer therapy-associated cardiovascular disease. Nat Rev Clin Oncol. 2016;13:172-184. doi: 10.1038/nrclinonc.2015.171.

36. Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, Ruddy KJ, Yan E, Redfield MM. Risk of Heart Failure With Preserved Ejection Fraction in Older Women After Contemporary Radiotherapy for Breast Cancer. Circulation. 2017;135:1388-1396. doi: 10.1161/CIRCULATIONAHA.116.025434.

37. Gyenes G, Fornander T, Carlens P, Rutqvist LE. Morbidity of ischemic heart disease in early breast cancer 15-20 years after adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 1994;28:1235-1241. doi: 10.1016/0360-3016(94)90500-2.

38. Walker V, Crijns A, Langendijk J, Spoor D, Vliegenthart R, Combs SE, Mayinger M, Eraso A, Guedea F, Fiuza M, Constantino S, Tamarat R, Laurier D, Ferrières J, Mousseaux E, Cardis E, Jacob S. Early Detection of Cardiovascular Changes After Radiotherapy for Breast Cancer: Protocol for a European

Multicenter Prospective Cohort Study (MEDIRAD EARLY HEART Study). 2018;7:e178. doi: 10.2196/resprot.9906.

Figure legend 1: Example of the contouring of the coronary arteries

The left ventricle (LV) was contoured using a multi-atlas automatic segmentation tool based on the delineations by Feng *et al.*. 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.

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

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

*: 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.

‡: non-rheumatic valve disorder included aortic stenosis and/or mitral valve insufficiency.

§: ischemic heart diseases included coronary atherosclerosis, myocardial infarction, unstable/stable angina pectoris.

Table 2: Tumor and treatment characteristics at the time of breast cancer diagnosis for all 109 breast cancer survivors	
Tumor characteristics (%)	
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)
Radiotherapy, 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 (%)	
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; T, tumor; N, nodes; Gy, gray; LV, left ventricle; LMCA, left main coronary artery; LAD, left anterior descending coronary artery; CX, circumflex coronary artery; RCA, right coronary artery

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

Variable		%
Left ventricle ejection fraction (%) based on 107 BC patients[*]		
Mean	58.04	
Range	41.00–71.00	
Missing	2	1.8
Abnormal left ventricle ejection fraction[†]		
Yes	15	13.8
No	92	84.4
Missing	2	1.8
Left ventricle global longitudinal strain (%) based on 52 BC patients[‡]		
Mean	-16.95	
Range	-23.26–-9.44	
Missing due to limited quality	57	52.3
Left ventricle diastolic function (cm/sec) based on 109 BC patients[§]		
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

Abbreviations: BC, breast cancer

[*]: measured left ventricle ejection fraction (LVEF) with biplane method of disks summation (modified Simpson's rule), if not available with eyeballing.

[†]: defined as a LVEF <54% according to the European Association for Cardio Vascular Imaging/American Society of Echocardiography.

[‡]: measured using automated two-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 RT. Results are based on 52 breast cancer survivors.

Variable	B	SE	95% CI for B	P-value*
D_{max} LMCA	0.883	0.342	0.195–1.570	0.013

Abbreviations: RT, radiotherapy; B, regression coefficient; SE, standard error; CI, confidence interval; D, dose; LMCA, left main coronary artery

* P-value between the variable and the endpoint GLS of the LV, calculated using lineair regression analysis.

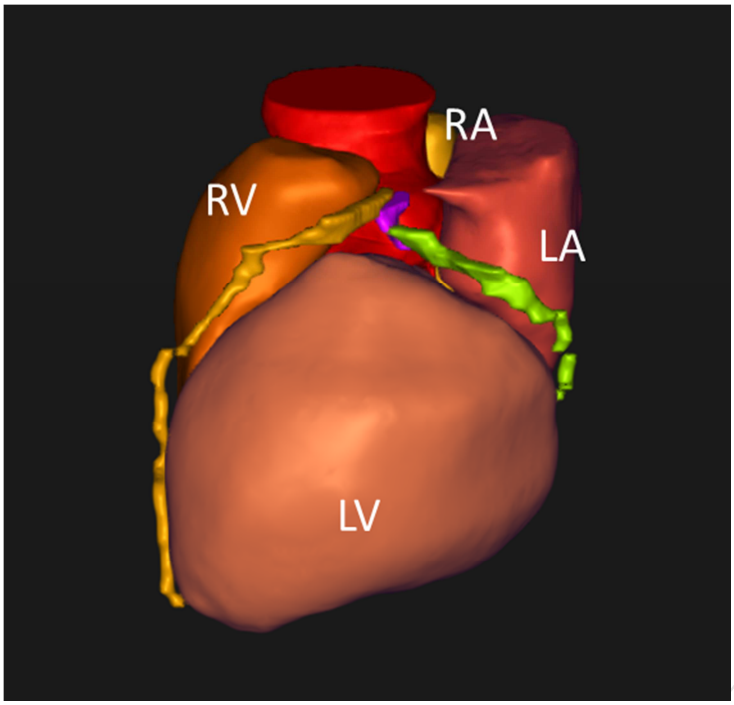
Table 5: Model characteristics of the final model for the endpoint diastolic function of the left ventricle in breast cancer survivors within first 10 years after RT. Results are based on 109 breast cancer survivors.

Variable	B	SE	95% CI for B	P-value*
Age at BC diagnosis	-0.155	0.021	-0.197–-0.133	0.000
Hypertension	-1.309	0.536	-2.372–-0.246	0.016

Abbreviations: RT, radiotherapy; B, regression coefficient; SE, standard error; CI, confidence interval

* P-value between the variable and the endpoint diastolic function of the LV, calculated using lineair regression analysis.

Figure 1:



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 post-operative radiotherapy (RT). The 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.