Author: Mast, Mirjam
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CHAPTER 3

Vascular heart damage before and after
whole breast irradiation

Preradiotherapy Calcium Scores of the Coronary Arteries in a Cohort of Women with Early-Stage Breast Cancer: A Comparison with a Cohort of Healthy Women

Mirjam Mast[a], Mark Heijenbrok[b], Anna Petoukhova[a], Astrid Scholten[c], Joop Schreur[d] and Henk Struikmans[a,c]

[a] Radiotherapy Centre West, The Hague, The Netherlands;
[b] Department of Radiology, Medical Center Haaglanden, The Hague, The Netherlands;
[c] Department of Clinical Oncology, Leiden University Medical Centre, Leiden, The Netherlands;
[d] Department of Cardiology, Medical Center Haaglanden, The Hague, The Netherlands

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Abstract

Purpose
Breast cancer radiotherapy has been associated with an increased risk of cardiac toxicity. However, no data are available on the probability of developing coronary artery disease (CAD) in breast cancer patients when compared with healthy women. Therefore, baseline coronary artery calcium (CAC) scores, as an accepted tool to predict CAD, were determined and compared with the CAC scores of a healthy, asymptomatic cohort, the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.

Materials and methods
Eighty consecutive patients with ductal carcinoma in situ or infiltrative breast cancer referred for radiotherapy after breast-conserving surgery were included in our study. Their cardiovascular risk profile was registered, and a 64 multislice CT scan was performed. The CAC scores of an unselected (Caucasian only) Radiotherapy Centre West (RCWEST) cohort, as well as of those of a selected (comorbidity and race adjusted) RCWEST cohort, were determined. The scores of both cohorts were compared with those of the female (Caucasian only) MESA cohort.

Results
For the unselected RCWEST cohort ($n = 62$) we found significant ($p < .01$) higher scores for women in the 55-64 age category compared with those of the MESA cohort. In the selected cohort ($n = 55$) the CAC scores of the women in the age category 55-64 were significantly ($p = .02$) higher compared with the MESA cohort. No significant differences were noted in the other age categories.

Conclusion
Both cohorts revealed that CAC scores in the 55-64 age category were significantly higher than the CAC scores in the asymptomatic (female) MESA population. These data suggest that breast cancer patients bear a higher risk of developing coronary heart disease before the start of radiotherapy. Therefore, measures to decrease cardiac dose further in breast cancer radiotherapy are even more important.

Introduction

According to the data of the Early Breast Cancer Trialists Collaborative Group, breast cancer radiotherapy, as it was administered in 1970-1990, was associated with an increased risk of fatal cardiovascular events (1). This finding was confirmed in a retrospective study in the Dutch Late Effects Breast Cancer cohort (2). Taylor et al. concluded that the heart dose from lefttangential radiotherapy had decreased considerably over the past 40 years. However, they also noted that for approximately half of left-sided patients, part of the heart still receives ≥20 Gy and found that the left anterior descending coronary artery, of all main coronary arteries, received the highest dose (3). Marks et al. found that the radiation induced heart perfusion defects are located in the anterior parts of the left ventricle (4). These data indicate that even today, left-sided breast cancer radiotherapy is potentially harmful to the heart, and specifically to the left anterior descending coronary artery. This is relevant because radiotherapy is frequently applied in the primary treatment of breast cancer. In a Dutch population-based study, it was shown that about 63% of women with breast cancer received radiotherapy as part of their primary treatment (5).

However, no data are available on the frequency of risk factors predicting the probability of coronary artery disease (CAD) for the group of women diagnosed with early-stage breast cancer before starting radiotherapy. Specifically, when compared with healthy women, no data are available on the number of CAC (i.e., coronary artery calcium, or CAC) deposits. Therefore, in our study, these baseline CAC scores were compared with the CAC scores of a healthy female population. In doing so, the CAC scores in 80 consecutive female breast cancer patients were compared with the CAC scores of a healthy, asymptomatic female cohort, the MESA cohort (6).

The reasons for the use of CAC scores in our study design were as follows: a number of studies concluded that the amount of calcium deposits in the coronary arteries predicts the risk of subsequent cardiovascular events in cases without symptomatic CAD (7-11). Furthermore, Pletcher et al. stated in their systematic review and meta-analyses that CAC is an independent predictor of CAD (7). Finally, it was suggested that CAC deposits can be useful in deciding whether further diagnostic testing is necessary in asymptomatic patients or patients with nonanginal chest pain and was shown that low-dose CT has proved to be a sensitive, noninvasive method for quantifying CAC deposits (8). With this study we attempted to identify differences in CAC scores for several cohorts to assess the risk on CAD before starting the radiation treatment.

Materials and methods

From September 2008 until October 2010, 80 women were included in this study. Consecutive patients with either ductal carcinoma in situ (<4 cm) or infiltrative breast cancer (<5 cm) and treated with breast-conserving surgery were considered eligible. If indicated, chemotherapy started after radiotherapy. The study was approved by the local ethical committee (Dutch southwestern region), and written informed consent was obtained for all participants. A low-dose, nongated 64 multislice CT scan, the Lightspeed VR 64-MSCT (GE, UK), was performed within 10-15 min. No intravenous contrast enhancement was used. The performed CT scan took place before the start of radiotherapy.
The overall CAC score consists of the sum of all the calcium lesions present in the left main artery, left anterior descending coronary artery, left circumflex artery, and right coronary artery and was estimated with a GE Advantage Workstation Volume (share 2,

version 4.4 (2007), rev. 1, DFOV 25 cm, pixel area 0.5 x 0.5 mm^2). The method we used was described by Agatston et al. (12). All scans were evaluated by one radiologist (MH) specialized in determining CAC scores. To determine the inter-observer variability of the CAC values, a random selection (n = 58) of the available CAC scans was done. A second radiologist, blinded to the scores of the first observer, determined for each of the 58 cases a second CAC score.

The MESA study was designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease in a population-based sample of 6,814 men and women aged 45-84 years. All participants were free of clinically apparent cardiovascular disease (6). To compare the results of the Radiotherapy Centre West (RCWEST) cohort to that of the MESA cohort, several risk factors of developing cardiac disease were registered. Age, height, body mass index (BMI, defined as weight in kilograms divided by height in square meters) and CAD risk factors: history of heart and vascular disease, including diabetes mellitus, hypertension, and hypercholesterolemia (the latter three only applicable when medication was used), were registered in specially designed questionnaires before starting the radiotherapy sessions. Smoking habits were registered and defined by the number of pack years. One pack year was defined by smoking a total of 20 cigarettes each day during 1 year. In the RCWEST cohort a woman was classified as a former smoker if she had stopped smoking more than one year before starting radiotherapy.

As a first step, the CAC scores of the Caucasian RCWEST cohort were compared with those of the (female) Caucasian MESA cohort. We then excluded patients suffering from diabetes mellitus and those diagnosed beforehand with cardiovascular diseases. By doing so, we created a cohort that was better comparable (specifically with respect to cardiac risk factors) to that of the MESA cohort. Finally, the CAC scores of this latter selected RCWEST cohort were compared with the (female) Caucasian MESA data. The calcium scores were classified into percentiles, e.g., the 25th percentile implies that 25% of all cases have a CAC value lower than the given value.

According to Bax et al. (13), the determined CAC values are categorized as follows: low-risk calcium scores—CAC values 0-100; medium-risk calcium scores—100 < CAC values <400; high-risk calcium scores—CAC values >400.
For optimal comparison with the MESA cohort, three age categories of patients were created: 45-54, 55-64, and 65-74.Two age categories of patients were excluded from our analysis because the youngest age group in our cohort (<45) is not included in the MESA cohort, and the oldest age group (75-84) consisted only of two patients.

Statistical analysis
Because the data were heavily skewed with 36% of the patients having a CAC score of zero, a log transformation was computed on all CAC values. On the log scale, the data were normally distributed. A paired t test was performed to determine the inter-observer variability of the overall CAC values. The inter-observer variability of the CAC values was also evaluated for each single artery (left main artery, left anterior descending coronary artery, left circumflex artery, and right coronary artery). A Wilcoxon signed rank test was performed for the latter analysis because the number of eligible data was <30. For a comparison of the RCWEST cohort to the MESA cohort, the distribution of the CAC scores was analyzed with the Chi-square test. The MESA CAC distribution for each age group was computed into a ratio (expected) and was compared to the CAC distribution of the RCWEST cohort (observed). A Chi-square test was also performed for the comparison of age, race, smoking, and BMI between both cohorts.

For analysis, we used SPSS Statistics version 17.0. The level of statistical significance was considered $p < 0.05$ for all tests. (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.)

Results

Eighty women diagnosed with either pure ductal carcinoma in situ (<4 cm; 5% of all cases) or infiltrative breast cancer (<5 cm; 95% of all cases) were included. Sixty-four percent of the women were postmenopausal. Thirteen percent of the patients in the RCWEST cohort had a history of cardiac disease; two patients had experienced a myocardial infarction in the past, and two patients mentioned that they had experienced signs of myocardial ischemia (angina pectoris). Furthermore, 8 patients suffered from diabetes mellitus. In three of these eight patients, a combination of the excluding factors were present. Seven patients were not Caucasian.

The mean age of the patients included in the RCWEST cohort was 56 years (range, 29-81), and for the MESA cohort, the mean age was 62 (range, 45-84). The mean BMI in the RCWEST cohort was 26 (range, 18-39); for the MESA cohort, no mean BMI was available. A significant difference between the RCWEST and the MESA cohort was found in the distribution of BMI categories; specifically, the BMI categories <25 and 30 to <40 seem to be different. A significant difference was also found for the age categories: in the RCWEST cohort, a higher percentage of women in the 55- to 64-year age category was included; in the MESA cohort, more women were included in the 45- to 54-year age category. Furthermore, the distribution of race was significantly different: in the RCWEST cohort, a larger number of Caucasian women was included. Finally, the smoking status of the RCWEST cohort differed significantly from those of the MESA cohort, specifically in the current smokers category (Table).
The mean overall CAC was 82 with a range of 0-779, with 53% of the CAC scores being zero.

Inter-observer variability CAC values
For 73% (n = 58) of the patients, the inter-observer variability between the two radiologists was evaluated. No significant differences ($p = 0.3$) in the overall CAC values were found. However, for each separate artery, it was difficult in some patients to determine to which artery the specific CAC value belonged. In these cases, the proportion of calcium deposits was situated near the bifurcation of two arteries. Both radiologists scored an overall CAC value of zero in the same patients.

Comparison with the MESA cohort
For the unselected Caucasian RCWEST cohort (n = 65; the 15 patients <45 and >74 were excluded, see Materials and methods) we found significantly ($p < 0.01$) higher CAC scores when compared to those of the (female) Caucasian MESA cohort. This applied specifically for the CAC distribution for women in the age category of 55-64 years old. In the other age categories, no significant differences were found (age category 45-54: $p = 0.84$; age category 65-74: $p = 0.07$).

Percentiles of CAC scores for three age categories of Caucasian patients only (45-54, 55-64, and 65-74; n = 62) are shown in the Figure for both the RCWEST cohort and the MESA cohort. These scores showed that in the 45-54 age category (n = 11), the numbers of patients with the value 0 were approximately the same (25th-75th percentile values), but the 95th percentile CAC value was higher in the MESA data. The CAC values of the RCWEST 55-64 age category (n = 33) increased more rapidly than the

MESA cohort, and the CAC values of the 65-74 age category (n = 18) seem to be of the same magnitude.

The selected RCWEST cohort was created by excluding the cases with a history of cardiac disease, diabetes mellitus, and non-Caucasians and consisted of 55 patients. This selected cohort also showed a significantly (p = 0.02) higher CAC distribution for the women in the 55-64 age category compared with that of the MESA cohort. For the other age categories, no significant differences were found.

	RCWEST (Number)	RCWEST (%)	MESA (%)	P-value	Selected RCWEST cohort
Age (years)					
< 45	13*	16.3	0	< 0.001	9*
45-54	13	16.3	30.1		11
55-64	33	41.3	27.7		27
65-74	19	23.8	28.6		17
75-84	2^	2.5	13.6		2^
Race					
Caucasian	73	91.3	40.2	< 0.001	66
Chinese	0	0	11.4		n.a.
Black	2	2.5	27.8		n.a.
Hispanic	1	1.3	20.6		n.a.
Hindustani	4	5	0		n.a.
Diabetes Mellitus (DM)					
Yes	6	7.5	n.a.	n.a.	n.a.
No	74	92.5	n.a.		n.a.
Hypertension$					
Yes	11	13.8	43.8	n.a.¥	19
No	67	83.8	56.2		47
Combined with DM	2	2.5	n.a.		n.a.
Smoking cigarettes					
Never	39	48.8	58.8	0.02	33
Former	23	28.8	29.2		25
Current	18	22.5	12.0		8
BMI (kg/m^2)					
< 25	34	42.5	31.8	0.02	31
25-<30	31	38.8	34.6		25
30-40	15	18.8	28.5		10
≥ 40	0	0	5.0		0

*Excluded from analysis, no data available in MESA cohort
^ Excluded from analysis, too few patients in RCWEST cohort
$ RCWEST cohort: Only if a patient received medication for hypertension
¥ N.a. since different definitions were used in both cohorts

Table. Patient characteristics of the unselected RCWEST, The MESA and the selected RCWEST cohort.

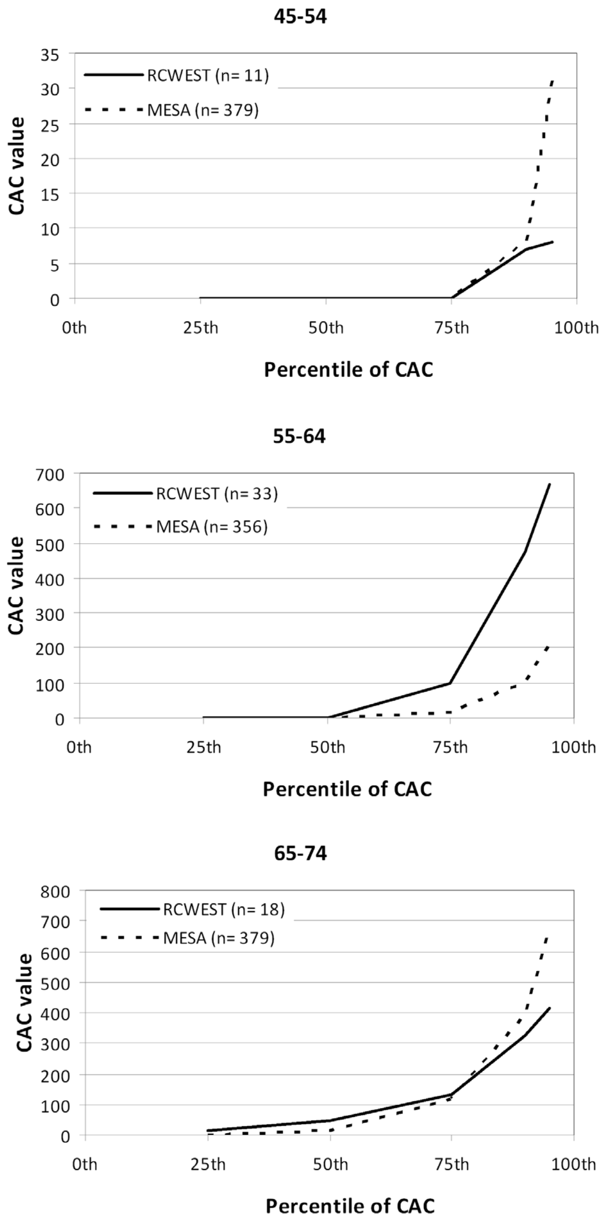

Figure. Percentiles of coronary artery calcium (CAC) scores for three Caucasian age categories (45-54, 55-64, and 65-74 years) for both the Radiotherapy Centre West (RCWEST) cohort (blackline) and the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (dashed line).

Discussion

A comorbidity and race adjusted comparison revealed that the RCWEST cohort CAC scores in the 55-64 age category were significantly higher than the CAC scores in the (asymptomatic) MESA cohort. This applies both to the unselected Caucasian RCWEST cohort and to the selected RCWEST cohort, in which only Caucasian and "healthy" patients were included.
However, to compare our data reliably to the MESA data, we needed to divide the cohort into specific age categories. Because the RCWEST cohort consisted of 80 women, this resulted in a small number of patients for each category. Therefore, the results of the chi-square test are less reliable. Possibly because of the small number of patients in the age categories 45-54 and 65-74, no differences were found compared with those of the MESA cohort (6).
Although we did not find significant differences between the observers, the determination of the CAC values for each separate artery was difficult in some patients. Therefore, we restricted ourselves by using the values of one radiologist and, in doing so, eliminated a possible inter-observer bias.

The number of CAC values of zero in the Caucasian RCWEST cohort was 44%, which is lower than the 62% in the MESA cohort of McClelland (6). Also, in the Caucasian RCWEST cohort, fewer women older than 65 had a CAC value of zero (50th percentile 46 for RCWEST and 13 for Caucasian MESA). This confirms the findings that significantly higher CAC values were found in one of the age categories of the RCWEST cohort.

According to Bax and colleagues (13), the relationship between CAC scores and CAD may be weakened because extensive calcification could possibly represent a more stable stage of CAD. Noncalcified and mixed lesions could be more vulnerable, but this is still a point of debate (14,15).

A drawback of our study is that we had to compare the Dutch RCWEST cohort with that of a healthy cohort, the American MESA cohort. However, no such data were available for the (healthy) Dutch female population. The MESA cohort consists of American women, and it is conceivable that those women experience different cardiac risk factors than Dutch women because of the different lifestyles in the United States (i.e., more dietary fat consumption, less physical activity, and higher BMI). Also, the number of current smokers in the RCWEST cohort is higher than in the MESA cohort; because we could not find the definition "formersmoker" in the MESA cohort, we applied the definition "smoker" if the patient had stopped less than 1 year before radiotherapy. Thereafter, we classified a patient as "former smoker" if the patient had stopped smoking without a time limitation. In that analysis, no significant differences were found between cohorts ($p = 0.18$). Furthermore, we compared our overall results for Caucasian women with those of the German Heinz Nixdorf Recall (HNR) study, a population-based study that recruited unselected participants in the German Ruhr area. This population would, theoretically, be better comparable to the Dutch RCWEST cohort, although the HNR study did not stratify for race (16). It was remarkable that in Caucasian women aged up to 60 years, the 50th percentile CAC values were all zero in both the HNR study and the RCWEST cohort.

However, in the selected RCWEST cohort, we found CAC 50th percentile values that were around 8 times higher compared with the HNR study (22 vs. 2.6) for Caucasian women in the 65-69 age category ($n = 15$). For this comparison, we again had to divide our group of patients into comparable age groups; in doing so, only a small number of patients remained in each age category.

As for the BMI, a BMI of >25 kg/m^2 is classified as overweight according to the World Health Organization guidelines. We found a smaller number of patients in the Dutch RCWEST cohort who could be classified as overweight (58%) than in the American MESA cohort (68%) (11), but we found higher BMI values in our study compared with the general Dutch female population according to Statistics Netherlands (CBS). In the Dutch female population aged ≥20 years old, the number of overweight patients in 2007 was 40% (17). However, the fact that the women in the RCWEST cohort experience a higher BMI compared with the Dutch female population corresponds to the finding that overweight is a risk factor for breast cancer. Remarkably, a BMI higher than 30 kg/m^2.seems to correlate with a worse disease-free survival in breast cancer patients (18, 19).

Because this cohort is not selected, our results might be representative of breast cancer patients treated with breastconserving therapy. Our study underlines the necessity to compare treatment associated CAD in patients with left-sided breast cancer with other cohorts of breast cancer patients, because those women may also eventually be more predisposed to develop CAD. In 2008, a heart-sparing breath-hold technique (20) was introduced in our department to decrease cardiac dose for leftsided breast cancer cases. We intend to quantify the efficacy of the heart-sparing technique by comparing the number of calcium deposits in the coronary arteries of breast cancer patients treated with and without use of the ABC technique before radiotherapy until 3 years after completion of the radiation treatment.

Conclusion

Despite the relatively small number of patients, the RCWEST cohorts revealed that the CAC scores in the 55-64 age category were significantly higher than the CAC scores in the asymptomatic (female) MESA cohort. These data suggest that breast cancer patients bear a higher risk of developing CAD. Therefore, measures to decrease cardiac dose further in breast cancer radiotherapyare even more important.

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Less increase of CT based calcium scores of the coronary arteries three years after breast-conserving radiotherapy using breath-hold

Mirjam Mast[a], Mark Heijenbrok[b], Loes van Kempen–Harteveld[a], Anna Petoukhova[a], Astrid Scholten[c], Ron Wolterbeek[d], Joop Schreur[e] and Henk Struikmans[a,f]

[a] Radiotherapy Centre West, The Hague, The Netherlands;
[b] Department of Radiology, Medical Center Haaglanden, The Hague, The Netherlands;
[c] Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[d] Leiden University Medical Centre, department of medical statistics and bioinformatics, Leiden, The Netherlands
[e] Department of Cardiology, Medical Center Haaglanden, The Hague, The Netherlands
[f] Department of Clinical Oncology, Leiden University Medical Centre, Leiden, The Netherlands;

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Summary

The aim of this prospective longitudinal study was to identify differences in Coronary Artery Calcium (CAC) scores between three groups of breast cancer patients (right-sided, left-sided treated with and without breath-hold) by comparing the CAC scores before the start of radiotherapy to those determined three years after radiotherapy. Breath-hold in breast-conserving radiotherapy leads to a less pronounced increase of CT based CAC scores.

Abstract

Purpose
The aim of this prospective longitudinal study was to identify differences in Coronary Artery Calcium (CAC) scores between three groups of breast cancer patients by comparing the CAC scores before the start of radiotherapy to those determined three years after radiotherapy.

Materials and methods
Multi-slice CT scans were carried out in 99 consecutive patients, referred for radiotherapy after breast-conserving surgery. No regional radiotherapy was given. The patients were subdivided in three groups: left- and right-sided radiotherapy, and left-sided radiotherapy using a breath-hold technique. The differences in increase of the overall and Left Anterior Descending (LAD) coronary artery CAC scores were determined. Within each patient the LAD minus RCA scores were also analyzed, representing the CAC scores of the LAD minus those of the Right Coronary Artery (RCA).

Results
After three years, a non-significant lower increase in overall CAC scores and a significant lower increase in mean CAC scores in the LAD was found for the group with left-sided breast cancer treated with breath-hold compared to the group without breath-hold. Furthermore, the LAD minus RCA scores in patients treated for left-sided breast cancer without breath-hold were higher when compared to those with right-sided breast cancers and those with left-sided breast cancer treated with breath-hold.

Conclusion
Breath-hold in breast-conserving radiotherapy leads to a less pronounced increase of CT based CAC scores. Therefore, breath-hold is probably useful to prevent the development of radiation-induced coronary artery disease. The drawbacks of our study were the small numbers and the relatively short follow-up period.

Introduction

Radiotherapy for left-sided breast cancer has been associated with an increased risk of Coronary Artery Disease (CAD) [1,2]. This rate of major coronary events started to increase within a period of 5 years of exposure of radiotherapy. Also was determined that the incidence of major coronary events was proportional to the mean dose to the heart [3]. Furthermore, Nilson et al. found a higher amount of calcium deposits in the LAD coronary artery after radiation therapy for left-sided breast cancer compared to the same situation for right-sided breast cancer [4]. Whetal et al. confirmed that the presence of radiation-induced calcium deposits is seen as a surrogate marker for radiation-induced atherosclerotic lesions. They found more atherosclerotic lesions in the LAD of irradiated Hodgkin's lymphoma survivors than in non-irradiated patients. These patients were treated with mediastinal or mantle field radiotherapy (including the pre-cranial arteries and/or coronary arteries) with a median dose of 40 Gy [5]. According to Greenland et al. and Oudkerk et al., the amount of calcium deposits in the coronary arteries (CAC scores) predicts the risk of subsequent cardiovascular events [6,7]. Another study showed that CAC scores, when compared with 11 other newer coronary heart disease risk markers, were the best predictors of the occurrence of cardiovascular disease in persons who were initially without CAD [8]. Moreover, it appeared that adding CAC scores to the Framingham Risk score (FRS) improved the accuracy of risk predictions [8]. It should be emphasized that the FRS is the most commonly used CAD risk prediction score [9].

To the best of our knowledge, no studies have been carried out that compared the amount of CAC before and after radiotherapy in breast cancer patients treated with radiotherapy. Therefore, we prospectively determined CAC scores at baseline as well as three years after radiotherapy in 99 consecutive female breast cancer patients receiving breast-conserving radiotherapy.

The aim of this prospective longitudinal study was to identify possible differences in CAC scores between patients irradiated for right-sided breast cancer and patients irradiated for left-sided breast cancer. The latter group comprised both patients irradiated using a breath-hold technique and those irradiated without using a breath-hold technique.

Materials and methods

Patients

Patients with either DCIS (< 4 cm) or breast cancer (< 5 cm) and treated with breast-conserving surgery and whole breast radiotherapy were considered eligible. No regional radiotherapy was given. Every eligible patient referred to our department, Radiotherapy Centre West (RCWEST), was asked to participate in this study. Seventy percent of all eligible patients agreed to participate. From September 2008 until July 2011, 109 consecutive patients were included in this prospective study. The study was approved by the local ethical committee (METC Zuidwest Holland). Written informed consent was obtained from all participants. If indicated, adjuvant systemic therapy and/or chemotherapy was given, starting after radiotherapy. Our patient population consisted of three groups: i) 21 patients treated with left-sided radiotherapy (group L-BH); ii) 23 patients treated with right-sided radiotherapy (group R); and iii) 65 patients treated with left-sided radiotherapy using a breath-hold technique (group L+BH). From January 2010 onwards, in all left-sided breast cancer patients in RCWEST the Active Breathing Control (ABC) breath-hold method [10,11] was used. Therefore, the third group (group L+BH), consisted of patients receiving radiotherapy using a breath-hold technique. Subsequently, from October 2010 hypofractionation schemes were routinely administered [12,13]. In 33 of these 65 left-sided breast cancer patients, treated with breath-hold, a hypofractionation scheme was used.

CAC CT scan
CAC CT scans were carried out at baseline and after three years. CAC was measured using non-contrast, low-dose non-gated cardiac CT studies on a GE 64-slice MDCT scanner (LightSpeed VCT, General Electric Medical System®, Milwaukee, WI). The non-invasive CT scan was performed within 10-15 minutes. A 2.5 mm reconstructed slice thickness was used.

The CAC score was calculated according to Agatston et al. [14]. The Agatston score requires three contiguous voxels of >130 Hounsfield units. The overall coronary calcium score was determined on a GE Advantage Workstation Volume (share 2, version 4.4 (2007), DFOV 25 cm, pixel size 0.5x0.5 mm^2), by summing individual lesion scores from each of the main epicardial coronary arteries: Left Main Artery (LMA), Left Anterior Descending (LAD) artery, Left Circumflex (LCX) artery, and Right Coronary Artery (RCA).

To avoid interobserver variations, all scans were evaluated by one radiologist (MH), specialized in determining CAC scores, and one cardiologist (JS), in order to reach a consensus on all calculated calcium scores. Both were blinded for the side of the radiotherapy (right of left breast). All scans were reviewed separately. When different scores were found, a joint review took place, and a final decision was reached based on consensus. CAC scores were categorized into three groups: i) a low-risk group: 0 – 100; ii) a medium risk group: 100-400; iii) a high-risk group: > 400 [15]. We compared the distribution of these three risk groups in time within each of the three patients groups: R, L-BH and L+BH.

Radiotherapy
Details on the patient position, the CT scan before the radiation treatment, the breath-hold technique and the delineation of the target and critical organs were described earlier [11]. A 3D-Conformal Radiation Therapy (3D-CRT) technique was used. Details about this technique and dose specification were also described earlier [11]. Total doses were: 50 Gy in 25 fractions for the conventionally fractionated cases, and 42.56 Gy in 16 fractions for the cases irradiated with a hypofractionation scheme. If indicated according to the national guidelines, a boost dose, using a photon based technique, was added to the tumor bed. This boost dose was given after completion of the whole breast irradiation. The boost doses ranged from 13.30 Gy-26 Gy, in 5 to 13 fractions respectively, see Table 1.

Risk factors
The following cardiac risk factors were obtained before starting radiotherapy: age, height, BMI (Body Mass Index, defined as weight in kilograms divided by height in square meters), postmenopausal status, smoking habits. Also, specific CAD risk factors were obtained: history of heart and vascular disease, including diabetes mellitus, hypertension and hypercholesterolemia (the latter three were only found applicable when medication was used).

CAC scores analyses
Since we were interested in the difference between the baseline score and the score three years after radiation therapy, the patients who were not able to undergo a CAC CT scan after three years were excluded from the CAC analyses.

Concerning the CAC scores we determined:

1. the (mean) overall CAC scores and the (mean) LAD CAC scores at baseline and at three years after radiation for group L-BH, group R and group L+BH.

2. the (mean) differences between CAC scores within each patient in the LAD and the RCA (LAD minus RCA CAC scores), at baseline and at three years after radiation, for the three groups. Representing the differences in the individual patient. The RCA is the coronary artery that receives the lowest dose when administering whole breast radiotherapy, since the RCA is lying furthest away from the radiation treatment fields, both in left-sided as well as right-sided breast cancer radiotherapy. Therefore, this artery was used as a reference.

Statistical analysis

A descriptive analysis of the change of the CAC scores in time was carried out, reporting the mean, median, standard deviation and Standard Error (SE). The presence or absence of statistical significance of categorical values was determined using the Chi-square test. We fitted mixed models for the various outcome variables assuming no differences at baseline, and carried out a one-way analysis of variance (ANOVA) for the continuous values. For analysis, we used SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). P-values ≤ 0.05 (two-sided) were considered statistically significant for all tests.

Results

General characteristics of the patients and risk factors
For all 109 women a baseline CAC score was calculated. After three years of follow-up, ten women were lost to follow-up since they had either died, suffered from metastases or had received cardiac vessel metal implants which seriously distorted the quality of the CAC CT images. Hence, after three years of follow-up, in 99 women both a baseline and a follow-up CAC score were available (see Table 3 for the range when the follow-up calcium CT scan had taken place).

Of the 99 women 12% were diagnosed with pure DCIS (<4 cm) and 88 % with breast cancer (< 5cm). Forty percent of the patients received adjuvant chemotherapy, the latter was anthracyline based in all patients, Table 1.

The mean age of the patients was 56 years (range 28-74). Patient and treatment characteristics are summarized in Table 1. Sixty-eight percent of all 99 women had a postmenopausal status at baseline; 83% of the left-sided breast cancer patients irradiated without breath-hold; 70% of the right-sided breast cancer patients; and 62% of the left-sided breast cancer patients irradiated with breath-hold. Of all the women 91% was Caucasian, 3% was Spanish, 2% was Black and 4% was Hindustani.

The mean BMI in the RCWEST cohort was 26 (range 18-39), corresponding with overweight on the BMI scale [16]. Seventeen percent in the total RCWEST cohort had a BMI higher or equal to 30, corresponding with obesity on the BMI scale [16].

Table 1		Mean age at RT (years)	Left/Right sided breast cancer	RT with ABC (yes/no)	RT dose (Gy)		RT boost dose (Gy)	Chemo-therapy
R	(n=20)	55.6 [39-71]	Right	no	50.00		16 (n=5) / 20 (n=3) / 26 (n=3)	6
L-BH	(n=18)	61.2 [44-74]	Left	no	50.00		16 (n=8) / 20 (n=1)	8
L+BH	(n=28)		Left	yes	50.00		16 (n= 13) / 20 (n=3)	26
	(n=1)		Left	Yes	42.00	*		
	(n=32)	54.3 [28 - 72]	Left	yes	42.56		13.30 (n=17) / 18.62 (n=3)	

* Radiotherapy stopped prematurely, hence the planned dose of 50 Gy was not given

Table 1: Patient and treatment characteristics of the three RCWEST groups.

Seventeen percent of the women were smoking before they started with the radiation treatment. Around 52% of the women had a smoking history with a mean number of history pack years of 11 (range 0 – 56). Also, before the start of the radiation therapy 20% of the women were used to drinking more than 2 units of alcohol each day, 27% of them less than 1 unit per day.

One patient had experienced a cardiac arrest in the past and two patients reported that they had experienced signs of angina pectoris in the past. During the follow-up period no coronary vascular events or other (new) heart diseases had been reported. Furthermore, 23 patients suffered from hypertension and eleven patients suffered from diabetes mellitus. No differences were seen between the three groups, see Table 2.

Table 2

Group (n = 99)	R (n=20)	L-BH (n=18)	L+BH (n=61)	p-value
Postmenopausal at baseline	14	15	38	p = 0.2
Smoking	3	2	12	p = 0.7
History pack years >= 10	10	8	24	p = 0.7
Alcohol; > 2 units per day	5	7	8	p = 0.05
BMI < 25	6	8	29	p = 0.4
BMI >= 25	14	10	32	
History of cardiac diseases *	3**	4	5	p = 0.3
Hypertension ***	5	5	13	p = 0.8
DM ***	4	1	6	p = 0.3

* mostly arrhythmias
** one patient with a cardiac arrest
** some patients suffer from both hypertension and DM

Table 2: Distribution of the risk factors in the three RCWEST groups. Calcium scores: mean scores LAD and overall score.

At baseline, a comparable distribution of the risk factors between the three groups: L-BH, R and L+BH, was noted, see Table 2. After three years, only a small non-significant shift was noted in the CAC risk distribution (p>0.1), Table 3.

Table 3		Baseline								3 years (1095 days) after RT **							
		Mean / median Calcium-score LAD	Range	Mean / median Calcium-score Overall	Range	CAC low risk*	CAC me-dium risk*	CAC high risk*	Percent-age with zero Cal-ciumscore Overall	Mean / median Calcium-score LAD	Range	Mean / median Calcium-score Overall	Range	CAC low risk*	CAC me-dium risk*	CAC high risk*	Percent-age with zero Cal-ciumscore Overall
R	(n=20)	14.5 / 0.0	0 - 105	80.1 / 0.0	0 - 825	n=17	n=1	n=2	60%	29.9 / 0.0	0 - 255	138.0 / 0.0	0 - 1334	n=16	n=2	n=2	55%
L-BH	(n=18)	49.3 / 6.5	0 - 334	75.2 /11.0	0 - 477	n=14	n=3	n=1	28%	77.3 / 9.5	0 - 634	138.3 / 25.5	0 - 1055	n=13	n=3	n=2	28%
L+BH	(n=61)	19.3 / 0.0	0 - 401	35.7 / 0.0	0 - 645	n=54	n=6	n=1	66%	28.8 / 0.0	0 - 509	64.9 / 0.0	0 - 1039	n=51	n=7	n=3	51%
						p-value = 0.4								p-value = 0.8			

* low-risk group: 0 – 100; medium risk group: 100-400; high-risk group: > 400

** R = mean 1165 (974-1399); L-BH = mean 1161 (960-1398); L+BH = mean 1094 (889-1337)

Table 3: Calcium scores (mean and median; range; CAC risk group; percentage of calcium score 'zero') in all patients at baseline and three years after radiation therapy.

The mean overall CAC score at baseline was 52 with a range of 0 - 825. For the LAD at baseline we found a mean CAC score of 24 (range 0 – 401). After three years, the mean overall CAC score was 93 (range 0 – 1334) and for the LAD the mean CAC score was 38 (range 0 - 634). For the three groups the mean and median calcium scores of the overall and the LAD score were summarized in Table 3.

After analyzing the three cohorts it became apparent that the increase in the LAD calcium scores after three years was higher in group L-BH, see Figure 1: red line in the left part of the Figure. The mean increase in CAC scores for the overall and the LAD score in all three cohorts is visualized in Figure 1.

In comparing the observed differences in calcium scores over time, less increased mean calcium scores were found for the left-sided breast cancer patients treated with breath-hold (group L+BH) and right-sided (R) breast cancer patients compared to left-sided patients treated without breath-hold (L-BH). For the overall CAC scores these changes were non-significant (p>0.10). For the LAD, comparing left-sided without breath-hold (L-BH) and right-sided breast cancer (R), no significant difference was found (p=0.2); for left-sided breast cancer patients treated with the breath-hold technique (L+BH) versus left-sided patients without the breath-hold technique (L-BH) a significant lower calcium score was found (p=0.04; 95%CI: -42.7 to -1.15).

Calcium scores: LAD minus RCA

Concerning the calcium scores in the LAD minus the RCA, we found significant differences in the three groups (p=0.03). Lower scores were observed in the group of patients treated for left-sided breast cancer with breath-hold (L+BH) compared to left-sided breast cancer patients treated without a breath-hold technique (L-BH). See Figure 2 for mean differences in LAD minus RCA scores between baseline and three years after radiotherapy.

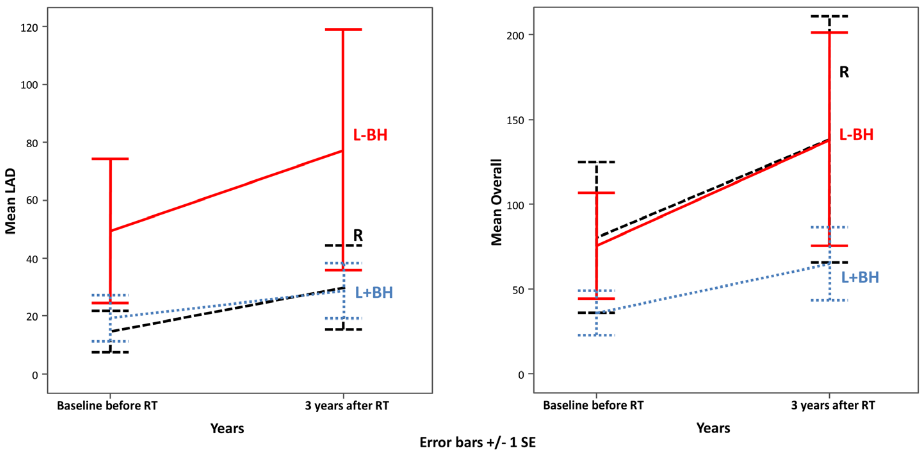

Figure 1: Mean calcium score increase in time with 1 Standard Error (SE) at baseline and at three years after radiotherapy. LAD score (left) and overall score (right); note: the scales in both Figures differ. Red solid line: Left-sided breast cancer patients, group L-BH. Black dashed line: Right-sided breast cancer patients, group R. Blue dotted line: Left-sided breast cancer patients treated in breath-hold, group L+BH.

Discussion

In this prospective longitudinal study we found a less pronounced increase in coronary artery calcium scores in patients with left-sided radiotherapy when using a breath-hold technique (L+BH) compared to those with left-sided radiotherapy without breath-hold (L-BH). Specifically with respect to the CAC scores of the Left Anterior Descending (LAD) coronary artery, this difference was statistically significant. Furthermore, three years after radiotherapy, significant differences were found for the CAC scores of the LAD minus the CAC scores of the RCA for left-sided breast cancer without breath-hold (L-BH), right-sided radiotherapy (R) and left-sided radiotherapy with breath-hold (L+BH). The increased CAC scores three years after radiotherapy, administered without a breath-hold technique, are indicative for a more pronounced development of (radiation-induced) atherosclerosis. These findings are consistent with the preclinical data of Stewart et al. [17]. They found that irradiation accelerates the development of macrophage-rich, inflammatory atherosclerotic lesions in carotid arteries of mice. Similar findings were reported by Schultz-Hector & Trott [18] and Basavaraju & Easterly [19].

Some drawbacks and strong points of our study should be mentioned.
In our cohort, the radiotherapy regimens were identical. As only breast-conserving radiotherapy was administered, regional radiotherapy was given in none of the patients. All patients were treated with 3D-conformal radiotherapy techniques in the same institute. The biological effective breast doses were identical [20, 21].

Drawbacks were the limited sample size of our cohort and the relatively short follow-up period of three years. Probably, larger differences will be found after a longer follow-up period. Whetal et al. did find an increased number of calcified and non-calcified artherosclerotic lesions of the pre-cranial artery in irradiated Hodgkin's lymphoma survivors (HLSs) [5]. The relative number of calcified lesions in the pre-cranial arteries of irradiated compared to non-irradiated patients they found was, however, comparable. The HLSs were examined 5-13 years after radiotherapy [5]. In this study no baseline CAC scores were determined; and the control group were non-irradiated patients referred for CT angiography of the pre-cranial arteries due to the suspicion of a recent stroke or TIA [5]. Conversely, Chang et al. performed coronary calcium CT scans in twenty asymptomatic breast cancer patients five to fourteen years after their radiation treatment. Chang et al. did not find increased calcium scores in left-sided breast cancer patients. The latter was probably due to the fact that most of them had a calcium score 'zero'; also, no baseline CAC values were available [22].

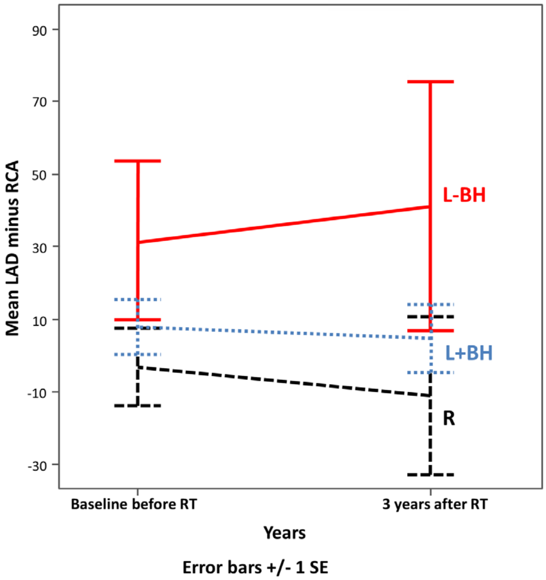

Figure 2: Mean CAC score: LAD minus RCA with 1 Standard Error (SE) at baseline and at three years after radiotherapy. Mean difference between baseline and 3 years after radiotherapy. Red solid line: Left-sided breast cancer patients (group L-BH). Black dashed line: Right-sided breast cancer patients (group R). Blue dotted line: Left-sided breast cancer patients treated in breath-hold (group L+BH).

Another drawback of our study was, that we did not investigate, for each individual patient, the relation between the amount of CAC and the delivered dose levels to the heart and the LAD. However, for a 3D conformal radiotherapy technique as well as for an IMRT technique without breath-hold, we have reported that the mean heart dose and the mean LAD dose could be decreased significantly by using a breath-hold technique [11]. These findings are in line with earlier reported decrease in LAD dose when using a breath-hold technique [23-26].

A strong point of our study was that the relevance of the use of the CT based CAC score is well supported by the literature. The CT based CAC score is known for its highly predictive value of developing cardiac vascular events. Kavousi et al. stated in 2012 that CAC scores even improved the Framingham Risk Score (FRS) predictions. However, they indicated that these scores may not be generalizable to younger or non-Caucasian populations. We want to stress that only very few non-Caucasian patients were included in our study. Besides this, although the mean age in the RCWEST groups was lower than that in the study performed by Kavousi et al., 56 years (SD 10.5) compared to 69.1 years (SD 8.5) respectively; the patients in our RCWEST cohort could not be classified as "young" [8].

Raggi et al. reported the relevance of low CAC scores. They found that a low CAC value was associated with higher survival rates (concerning all cause death) in all ages [27]. Also, a systematic review stated that the absence of an increased CAC score was associated with a low risk of future cardiovascular events [28].
In the RCWEST patients, it was not possible to calculate the FRS, since we did not measure the serum cholesterol levels and blood pressure.

A potential drawback seemed to be the differences of the CAC scores 'zero' between the three groups. Three years after radiotherapy 55% of the right-sided breast cancer patients of RCWEST still had a CAC score 'zero'. In the left-sided breast cancer patients it was 28% and in the left-sided breast cancer patients treated with a breath-hold technique it was 51%, see Table 2. The cohort of left-sided breast cancer patients treated with breath-hold consisted of relatively many patients with a CAC score 'zero' at baseline, i.e. 66%. With respect to these findings we want to emphasize that every consecutive patient was asked to participate in this study and that about 70% agreed to participate. Findings mentioned above can, therefore, be interpreted as a coincidence. The risk factors for cardiovascular disease in the three RCWEST patient groups (L-BH, R and L+BH) were comparable, including the CAC risk distribution, Tables 2 and 3. We found small differences in age and postmenopausal status at baseline, we therefore added the LAD minus RCA value in the analysis. This value represents the differences in CAC scores in the individual patient.

According to these findings summarized above we suggest that decreasing the heart dose in radiotherapy would be of great importance in breast cancer patients.

Conclusion

Breath-hold in breast-conserving radiotherapy leads to less increase in time of CT based CAC scores. A breath-hold technique therefore is probably useful to protect left-sided breast cancer patients against the development of radiation induced coronary artery disease. Drawbacks of our study are the small numbers and the relatively short follow-up period.

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