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Original article

Is the coronary artery calcium score associated with acute coronary events in breast cancer patients treated with radiotherapy?

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Background and purpose: The main objective of this study was to test whether pre-treatment coronary artery calcium (CAC) was associated with the cumulative incidence of acute coronary events (ACE) among breast cancer (BC) patients treated with postoperative radiotherapy (RT).
Material and methods: The study population consisted of 939 consecutive female BC patients treated with RT. The association between CAC and ACE was tested using Cox-proportional hazard models. Known risk factors for ACE and the mean heart dose (MHD), collected from three-dimensional computed tomography planning data, were tested for confounding.
Results: CAC scores varied from 0 to 2,859 (mean 27.3). The 9-year cumulative incidence of ACE was 3.2%, this was significantly associated with the pre-treatment CAC score. After correction for confounders, age, history of ischemic heart disease, diabetes, Body Mass Index $\geq$30, MHD, hypercholesterolemia and hypertension, the hazard ratio for ACE for the low and the combined intermediate and high CAC score category were 1.42 (95%CI: 0.49–4.17; $p = 0.519$) and 4.95 (95%CI: 1.69–14.53; $p = 0.004$) respectively, compared to the CAC zero category.
Conclusions: High pre-treatment CAC is associated with ACE in BC patients treated with postoperative RT, even after correction for confounding factors such as MHD.

Survival rates of breast cancer (BC) patients have gradually improved [1]. This improvement in survival is partly due to intensified treatment, such as radiotherapy (RT) and the use of more effective systemic agents [2,3]. Due to these higher survival rates, more BC patients are at risk of developing treatment-related side effects, such as radiation-induced cardiac toxicity. Although the introduction of more advanced radiation techniques has led to a substantial decrease in the radiation dose to the heart, in some cases the heart still receives a considerable radiation dose, which may contribute to the development of cardiac toxicity [4]. Recent studies showed that the risk of acute coronary events (ACE) in the first 9 years of follow-up increases by ~16% per Gray (Gy) of mean heart dose (MHD) [5,6]. These studies also indicated that the absolute excess risk induced by RT strongly depends on baseline cardiovascular risk factors. Therefore, it becomes increasingly important for radiation oncologists to identify which baseline factors are important for BC patients. This will facilitate calculation of the absolute excess risk of radiation-induced ACE in individual patients. This information can be used to select BC patients for primary or secondary preventive measures.

The amount of coronary artery calcium (CAC), as determined from Computed tomography (CT), is a well-established and reliable early predictor of ACE in the general population [7–9]. To establish the amount of CAC, deposits of calcium in the coronary arteries are quantified according to the Agatston score (AS) [10]. Higher CAC scores correspond to a higher risk of ACE [7–10]. In general, CAC is measured using diagnostic electrocardiogram (ECG) triggered CT scans. However, CAC scores can be obtained using non-triggered CT scans as well [11–15]. For RT treatment planning, BC patients generally undergo a non-triggered CT scan, which can be used to determine the baseline CAC value.

The main objective of this study was to test the hypothesis that pre-treatment CAC scores, based on non-triggered planning CT scans, are associated with the cumulative incidence of ACE among BC patients treated with postoperative RT.

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Material and methods

Study population

The population of this retrospective study was composed of a consecutive series of female BC patients who were treated between January 2005 and December 2008 at the University Medical Center, Groningen, The Netherlands. These patients were treated for invasive BC stages I-III or ductal carcinoma in situ (DCIS). Treatment consisted of curative breast-conserving surgery followed by RT. A dose of 50.4 Gy was prescribed for the whole breast in 28 fractions, with a simultaneous integrated boost dose of 14 or 16.8 Gy in the same 28 fractions, depending on pathologic risk factors [6]. Patients were only included if their treatment planning CT scans made prior to RT were available. Patients were excluded if they had a medical history of cancer (except for non-melanoma skin cancer) or had received prior RT or prior chemotherapy treatment. Patients with a history of cardiac disease were not excluded due to the fact that our aim was to develop an association model applicable to the general BC population. In contrast to a prediction model, an association model only describes the relationship between one predictor (i.e. CAC score) and the outcome (i.e. ACE) after correction for confounding factors. Patient characteristics, follow up data, information on cardiovascular risk factors and ACE were retrospectively extracted from patient hospital records. Missing data were supplemented with information derived from the general practitioner records after obtaining written informed consent from the surviving patients. Information about deceased patients was provided by the general practitioners, as in accordance with Dutch regulations. The following baseline patient characteristics were included in the analysis: age, history of ischemic heart disease (International Classification of Diseases, 10th Revision [ICD-10] codes I20-I25), other heart diseases (ICD-10 codes I30-I52), diabetes of any type (ICD-10 E10-E14), chronic obstructive pulmonary disease (COPD) of any type (ICD-10 J44), smoking status, body mass index (BMI), hypertension (ICD-10 I10-I15), hypercholesterolemia (ICD-10 E78.0) and the MHD. Ischemic heart disease, other heart disease, diabetes and COPD were considered when the diagnosis was stated in patients' medical charts. Smoking status was stratified into currently smoking or not smoking at baseline. BMI was stratified into two categories <30 and $\geq$30 kg/m^2. Hypertension was considered when diagnosis was stated (systolic blood pressure $\geq$140 mmHg and/or when diastolic blood pressure $\geq$90 mmHg) or when antihypertensive medication was used. Hypercholesterolemia was considered present if identified at clinical diagnosis or when statins were used (unless they were preventively used because of present cardiovascular risk factors such as diabetes). The MHD in Gray (Gy) was collected from three-dimensional (3D) conformal RT treatment plans based on the individual planning CT scans. The primary endpoint was the occurrence of ACE defined as diagnosis of myocardial infarction (ICD-10 I21-I24), coronary revascularization or death from ischemic heart disease (ICD-10 I20-I25). The study design was approved by the medical ethics committee of the University Medical Center Groningen.

Data collection and procedures

The CT scans used in this study were non-triggered CT scans (SOMATOM Sensation Open, 40 slice, Siemens Medical Inc.) acquired for RT treatment planning. The scanning protocol for the planning CT scans was different from that used in a dedicated CAC scan procedure, mandating correction of the CAC scores. For the correction of the CAC scores, a thorax phantom with calibration inserts was scanned (QRM Thorax & QRM-CCI, QRM, Germany) according to both the diagnostic CAC protocol and the RT planning CT protocol (Supplementary material Table 1). Rings of fat were placed around the phantom to represent patients of medium and large size [16]. Thereafter, the different amounts of calcium per calcium insert were determined from the multiple CT scans and quantified with the Aquarius software (iNtuition edition, v4.4.11.412.8585, Tera Recon, Inc.) according to the AS. Settings for the Aquarius software can be found in the supplementary material Table 2. The correction formula was obtained by plotting the CAC scores from the calcium inserts of the QRM phantom from the planning CT scan against that of the diagnostic scan (Supplementary material: Table 3 and Figs. 1–4).

To establish the CAC scores of the BC patients, the calcified lesions were selected and labeled per coronary artery by hand by a single trained technician. Subsequently, the software calculated the total CAC score. For patients with planning CT scans on which CAC was difficult to assess, experienced researchers of the Radiology department were consulted. Although patients with coronary stents and/or surgical clips due to cardiac surgery are at higher risk of ACE, these patients had to be excluded because CAC measurements were not possible due to artifacts. The CAC scores of the BC cohort were transformed using the correlation formulas described above (Supplementary material Table 3). The formulas were only used for patients with a CAC score higher than zero.

Statistics

To provide clinically relevant and easily applicable results, we first classified the CAC score into widely used clinical CAC score categories: CAC zero (0), low CAC (>0 – <100), intermediate CAC (100–400) and high CAC ($\geq$400) [7,15,17–20]. However, due to limited number of events in the high CAC score category we combined the intermediate and high CAC into one variable to maintain sufficient statistical power.

The cumulative incidence of ACE was calculated from the date of the first RT treatment using the Kaplan Meier method. Patients were censored when receiving a new radiation treatment, at time of death or at the end of the follow-up period.

The association between the CAC score and the cumulative incidence of ACE was first tested with a univariable Cox-regression analysis. Thereafter, all cardiovascular risk factors and the MHD were examined as possible confounders in a multivariable Cox-regression association model with the CAC score category as the main determinant. This was done by iteratively adding these risk factors to the univariable Cox-regression analysis. The risk factor that caused the largest change in the regression coefficients of the determinant (with a minimum of 10%) was selected as a confounder. This process was repeated with the remaining risk factors until the change in regression coefficients of the determinant was less than 10%. Data were analyzed using SPSS (IBM SPSS Statistics, Version 22, IBM Corp).

Results

Patient characteristics

The consecutive BC cohort consisted of 1,032 eligible patients. Fifty-six patients were excluded because they had been scanned with a different CT scanner, 8 because of missing CT data, 23 because of deviating CT scan protocol and 6 patients were excluded because their coronary stents caused too many artifacts for reliable CAC scoring. Eventually, a total of 939 patients were included in the analysis (Table 1). The mean age was 58.4 years (range: 26–84 years). The median follow-up was 7.5 years. The CAC scores were highly skewed and ranged from 0 to 2,859, with a mean CAC score of 27.3 and a median of 0. Most patients (78.9%) were

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