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Clinical Investigation

The Importance of Radiation Dose to the Atherosclerotic Plaque in the Left Anterior Descending Coronary Artery for Radiation-Induced Cardiac Toxicity of Breast Cancer Patients?

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Purpose: Radiation-induced acute coronary events (ACEs) may occur as a treatment-related late adverse effect of breast cancer (BC) radiation. However, the underlying mechanisms behind this radiation-induced cardiac disease remain to be determined. The objective of this study was to test the hypothesis that radiation dose to calcified atherosclerotic plaques in the left anterior descending coronary artery (LAD) is a better predictor for ACEs than radiation dose to the whole heart or left ventricle in patients with BC treated with radiation therapy.

Methods and Materials: The study cohort consisted of 910 patients with BC treated with postoperative radiation therapy after breast-conserving surgery. In total, 163 patients had an atherosclerotic plaque in the LAD. The endpoint was the occurrence of an ACE after treatment. For each individual patient, the mean heart dose, volume of the left ventricle receiving ≥5 Gy (LV-V5), mean LAD dose, and mean dose to calcified atherosclerotic plaques in the LAD, if present, were acquired based on planning computed tomography scans. Cox regression analysis was used to analyze the effects on the cumulative incidence of ACEs.

Results: The median follow-up time was 9.2 years (range, 0.1-14.3 years). In total, 38 patients (4.2%) developed an ACE during follow-up. For patients with an atherosclerotic plaque (n = 163), the mean dose to the atherosclerotic plaque was the strongest predictor for ACEs, even after correction for cardiovascular risk factors (hazard ratio [HR], 1.269; 95% CI, 1.090-1.477; $P = .002$). The LV-V5 was associated with ACEs in patients without atherosclerotic plaques in the LAD (n = 680) (HR, 1.021; 95% CI, 1.003-1.039; $P = .023$).

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: The results of this study suggest that radiation dose to pre-existing calcified atherosclerotic plaques in the LAD is strongly associated with the development of ACEs in patients with BC.

Introduction

The use of radiation therapy (RT) for the treatment of breast cancer (BC), combined with improved survival rates, has contributed to a growing population of BC survivors at risk of radiation-induced cardiac diseases.[1,2] One such disease is radiation-induced acute coronary events (ACEs), which have been extensively investigated. Several studies have shown a relationship between radiation dose to the heart and the risk of ACEs.[3,4] Furthermore, the results of a previous study suggested that the dose-effect relationship for ACEs could be improved by using the volume of the left ventricle receiving ≥5 Gy (LV-V5) instead of the mean heart dose (MHD).[4] However, clear understanding of the underlying mechanisms behind radiation-induced cardiac diseases is still lacking.

Studies have revealed anterior cardiac perfusion defects between 6 months and 20 years after BC-RT in areas that received a high radiation dose.[5-8] Sections of the anterior surface of the heart usually receive considerable radiation dose, >20 Gy in some patients, even when modern radiation techniques are used.[9] This area usually includes the left anterior descending coronary artery (LAD). However, limited data exist on the relationship between radiation dose to the coronary arteries and clinical events.

Several studies have shown a direct link between radiation dose and the location of coronary artery stenosis, mostly found in the LAD, after a median follow-up time of 10 to 12 years, suggesting accelerated atherosclerosis in areas receiving higher radiation dose.[10,11] However, no information was available concerning the presence of coronary artery stenosis before radiation. Based on in vitro models and limited autopsy findings, radiation-induced plaques tend to grow, rupture, and develop into myocardial infarctions or cerebrovascular accidents more often than stable, "age-related" collagenous plaques.[12,13] In addition, other researchers have found that irradiation accelerates the development of macrophage-rich, inflammatory atherosclerotic lesions and that these lesions are prone to intraplaque hemorrhage.[14,15] However, the effect of radiation to pre-existing atherosclerotic plaques in patients with BC is largely unknown.

We hypothesized that higher radiation dose to pre-existing atherosclerotic plaques in the coronary arteries increases the risk of ACEs, possibly owing to inflammatory reactions and subsequent plaque rupture and thrombosis. The objective of this study was to test the hypothesis that radiation dose to calcified atherosclerotic plaques is a better predictor for ACEs than radiation dose to the whole heart, left ventricle (LV), or LAD in patients with BC treated with 3-dimensional conformal RT.

Methods and Materials

Study population

The study population originated from a previously published study[4] and consisted of patients for whom follow-up data were updated. For surviving patients, general practitioners (GPs) were approached for a second time, and new data were also extracted from patient hospital charts.

The study cohort consisted of 910 female patients with BC treated with RT after breast-conserving surgery for stage I to III invasive adenocarcinoma or carcinoma in situ from January 2005 to December 2008 at the University Medical Center, Groningen, The Netherlands.[4] Only patients with RT planning computed tomography (CT) scans were included. Patients with a history of other malignancies (except nonmelanoma skin cancer) that required adjuvant treatment with systemic therapy or RT were excluded. The primary endpoint was an ACE, characterized as a diagnosis of myocardial infarction (International Classification of Diseases, 10th Revision, codes 121-124), coronary revascularization, or death resulting from ischemic heart disease (codes 120-125) after completion of BC-RT.

Data collection

Patient characteristics, medical history and cardiac risk factors (eg, history of ischemic heart disease, other cardiac diseases, hypertension, hypercholesterolemia, diabetes, body mass index ≥ 30 kg/m^2, and current smoker status), tumor characteristics, treatment plans, and follow-up data were extracted from patient hospital records. Missing data were supplemented after obtaining written informed consent from the surviving patients with BC, with information from GP records. Information about deceased patients was provided by the GPs, in accordance with Dutch regulations.

For every patient, a coronary artery calcium (CAC) score was determined from the planning CT scan with the use of a software tool, Aquarius (iNtuition edition, version 4.4.11.412.8585, TeraRecon, Inc). To establish the CAC scores, calcified lesions in the LAD (with Hounsfield units between 130 and 1300) were selected and labeled 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 from the radiology department were consulted. This method has been reported previously.[16] The location of the plaque was determined for patients with a positive CAC score (ie, the proximal, middle, or distal part of the LAD).

The date of enrollment was the first day of breast irradiation. Patients were registered for death or incidences of a new treatment with radiation and/or chemotherapy, either during or at the end of the follow-up period. The follow-up period was defined as the time between baseline and event or registration date. Patient information was collected until the date of either the last known GP information or the last medical follow-up. According to the Dutch legislation, the medical ethics committee of the University Medical Center Groningen did not need to approve this study. This was confirmed with the medical ethics committee and recorded in a written statement. The recruitment of patients and the informed-consent procedure were checked and approved by the legal department of the University Medical Center Groningen.

Radiation dosimetry

All patients were treated with 3-dimensional conformal RT using CT-based treatment planning, as described previously.[17] 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.

The whole heart, right ventricle (RV), and LV were contoured using an atlas, generated in-house, for free-breathing, noncontrast CT scans. The atlas was created using an atlas-based auto-segmentation (ABAS) routine in Mirada RTx, version 1.6 (Mirada Medical, Oxford, UK) according to definitions by Feng et al.[18,19] However, the ABAS algorithm was not a valid and reliable method to contour the small LAD automatically.[19,20] Therefore, an in-house automatic segmentation tool was developed for the LAD delineation based on anatomic landmarks. This tool automatically delineated a circle (diameter 5 mm) in the anterior interventricular groove, based on contours of the RV and LV generated by the ABAS routine. For details regarding the LAD auto-segmentation method, refer to our recent publication.[21] The auto-segmentation tool was expanded, whereby the LAD was divided into 3 parts—proximal, middle, and distal—according to guidelines outlined by Duane et al (an example is shown in Fig. E1).[22] For every patient with a positive CAC score in the LAD, all calcified atherosclerotic plaques with Hounsfield units between 130 and 1300 were manually delineated on the planning CT scans.[16,23]

The next step was to register, for each patient's RT plan, the MHD, LV-V5, mean LAD dose (including the mean dose to the proximal, middle, and distal parts), and the mean dose to the LAD atherosclerotic plaque (in case of multiple plaques, all plaques were delineated as 1 structure, and 1 mean dose was calculated). Dose-volume histograms were calculated, and the relevant dose-volume parameters were recorded per RT plan.

Statistical methods

The Kaplan-Meier method was used to analyze the cumulative incidence of ACEs. Fractional polynomials in R, version 1.1.463 (RStudio, Inc, 2009-2018), were used to test the linearity of the relationship between the continuous dose-volume parameters and the endpoint in univariable Cox regression. All parameters showed a linear relationship, so no transformations were required. With the calculated dose per patient, a dose-effect relationship could be determined independently of RT technique or treatment volume. Heterogeneity in cardiac dose distributions is needed to describe the relationship between dose to cardiac substructures and ACEs. Therefore, patients with right-sided BC and patients with left-sided BC both have to be included to obtain a wide range of dose levels to the different cardiac substructures for the analysis on dose-effect relationships. To examine a possible relationship among the MHD, the LV-V5, the mean LAD dose, and the mean dose to the atherosclerotic plaque in the LAD and the occurrence of an ACE, a Cox regression analysis was used. In addition, the relationship between the maximum dose to the LAD and its atherosclerotic plaque and the cumulative incidence of ACEs was also investigated. Furthermore, we analyzed the excess risk of an ACE due to RT in univariable and multivariable analysis. For the multivariable analysis, the relationship between dose and ACEs was corrected for cardiovascular risk factors that were significantly different between the groups of patients with and without an atherosclerotic plaque, including age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes. The excess risk was shown in a Cox regression curve. Calculations were performed with the use of SPSS software (IBM SPSS Statistics, Version 22, IBM Corp).

Results

Patient characteristics

The patient characteristics at baseline for the entire study cohort and for patients with and without an atherosclerotic plaque in the LAD are shown in Table 1. The median follow-up time was 9.2 years (range, 0.1-14.3 years). Of the 910 patients with BC, 843 (92.6%) were eligible for CAC scoring (the flowchart is shown in the Figure ES2). In total, 163 patients had a pre-existing atherosclerotic plaque in the LAD. Of those 163 patients, most plaques occurred in the proximal part of the LAD (96.9%). In 43 patients (26.4%), the plaque occurred in the middle part of the LAD. Plaques in the distal part of the LAD were rare (1.8%).

In total, 38 patients (4.2%) developed an ACE during follow-up. In the patient group with an atherosclerotic plaque, 19 patients (11.7%) developed an ACE, which

Table 1 Patient characteristics at time of breast cancer diagnosis

Characteristic	Totalcohort (n = 910)	Patients with atherosclerotic plaque (n = 163)	Patients without atherosclerotic plaque (n = 680)	*P**
Age at breast cancer diagnosis, median (range), y	59 (26-84)	68 (39-84)	57 (26-84)	<.001
Follow-up time, median (range), y	9.2 (0.1-14.3)	8.4 (0.4-13.8)	9.2 (0.1-14.3)	.001
History of cardiac comorbidity, n (%)				
Ischemic heart disease†				<.001
Yes	35 (3.8)	17 (10.4)	14 (2.1)	
No	875 (96.2)	146 (89.6)	666 (97.9)	
Other heart disease‡				.08
Yes	31 (3.4)	9 (5.5)	19 (2.8)	
No	879 (96.6)	154 (94.5)	661 (97.2)	
Hypertension§				<.001
Yes	273 (30.0)	78 (47.9)	178 (26.2)	
No	637 (70.0)	85 (52.1)	502 (73.8)	<.001
Hypercholesterolemia‖				
Yes	141 (15.5)	48 (29.4)	85 (12.5)	
No	769 (84.5)	115 (70.6)	595 (87.5)	
Diabetes¶				.001
Yes	65 (7.1)	21 (12.9)	39 (5.7)	
No	845 (92.9)	142 (87.1)	641 (94.3)	
Lifestyle risk factors (%)				
Active smoking#				0.50
Yes	200 (22.0)	32 (19.6)	150 (22.1)	
No	710 (78.0)	131 (80.4)	530 (77.9)	
BMI ≥30 kg/m^2				0.26
Yes	84 (9.2)	12 (7.4)	70 (10.3)	
No	826 (90.8)	151 (92.6)	610 (89.7)	
Coronary artery calcium score in LAD**				n/a
Median	0.00	40.07	0.00	
Range	0.00-1924	1.87-1923.68	0.00-0.00	
Excluded patients (%)	67 (7.4)	0 (0.0)	0 (0.0)	
Atherosclerotic plaque in LAD (%)				
Plaque in proximal LAD				n/a
Yes	n/a	158 (96.9)	n/a	
No	n/a	5 (3.1)	n/a	
Plaque in mid-LAD				n/a
Yes	n/a	43 (26.4)	n/a	
No	n/a	120 (73.6)	n/a	
Plaque in distal LAD				n/a
Yes	n/a	3 (1.8)	n/a	
No	n/a	160 (98.2)	n/a	
Tumor characteristics (%)				
Pathologic T stage				
T1	667 (73.3)	123 (75.5)	495 (72.8)	0.49
T≥2	238 (26.2)	39 (23.9)	181 (26.6)	0.48
Unknown	5 (0.5)	1 (0.6)	4 (0.6)	
Pathologic N stage				
N0	632 (69.5)	112 (68.7)	468 (68.8)	0.98
N1	195 (21.4)	30 (18.4)	151 (22.2)	0.29
N2	46 (5.1)	10 (6.1)	36 (5.3)	0.67
N3	7 (0.8)	2 (1.2)	5 (0.7)	0.53
Nx/Unknown	30 (3.3)	9 (5.5)	20 (2.9)	
Laterality of the breast cancer (%)				0.11
Right	459 (50.4)	74 (45.4)	356 (52.4)	
Left	451 (49.6)	89 (54.6)	324 (47.6)	

(*Continued*)

Table 1 (*Continued*)

Characteristic	Totalcohort (n = 910)	Patients with atherosclerotic plaque (n = 163)	Patients without atherosclerotic plaque (n = 680)	P*
Systemic treatment of breast cancer (%)				
Chemotherapy††				<0.001
Yes	334 (36.7)	26 (16.0)	288 (42.4)	
No	576 (63.3)	137 (84.0)	392 (57.6)	
Hormonal therapy				0.725
Yes	386 (42.4)	68 (41.7)	294 (43.2)	
No	524 (57.6)	95 (58.3)	386 (56.8)	
Trastuzumab				0.786
Yes	47 (5.2)	8 (4.9)	37 (5.4)	
No	863 (94.8)	155 (95.1)	643 (94.6)	
Radiation therapy, Gy				
Mean heart dose				0.490
Median	2.35	2.73	2.27	
Range	0.51-15.25	0.69-10.99	0.51-15.25	
Volume of LV receiving ≥5 Gy (%)				0.281
Median	1.04	9.93	0.00	
Range	0.00-100.0	0.00-98.77	0.00-100.0	
Mean dose, LAD				0.579
Median	2.82	7.51	1.80	
Range	0.41-59.33	0.41-51.52	0.43-59.33	
Mean dose, proximal LAD				0.808
Median	3.22	4.04	2.30	
Range	0.37-60.91	0.38-60.70	0.42-53.18	
Mean dose, mid-LAD				0.452
Median	3.39	7.82	2.00	
Range	0.41- 62.07	0.44-56.38	0.46-61.26	
Mean dose, distal LAD				0.735
Median	2.26	6.13	1.55	
Range	0.36-60.89	0.38-50.89	0.37-60.89	
Mean dose, atherosclerotic plaque LAD‡‡				n/a
Median	n/a	2.37	n/a	
Range	n/a	0.41-13.49	n/a	

Of the 910 BC patients included in this study, 843 patients were eligible for calculating the CAC score; 67 patients had to be excluded owing to artifacts or had been scanned with a different computed tomography (CT) scanner or were excluded owing to a deviating CT-scan protocol.

Abbreviations: BMI = body mass index; CAC = coronary artery calcium; LAD = left anterior descending coronary artery; LV = left ventricle; N = nodal; T = tumor.

* The *P* value was calculated between patients with (n = 163) and without (n = 680) an atherosclerotic plaque using an independent-sample *t* test or χ^2 test, as appropriate.

† History of ischemic heart disease was defined as myocardial infarction or angina.

‡ Other heart disease indicates heart failure, valvular heart disease, or myocarditis/pericarditis was stated in the patient's medical record.

§ Hypertension was determined when the systolic blood pressure was ≥140 mm Hg and/or when the diastolic blood pressure was ≥90 mm Hg, when antihypertensive medication was used, or when the diagnosis was stated in the patient's medical record.

‖ 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).

¶ Diabetes (of any type) was considered when the diagnosis was stated in patients' medical charts.

Smoking status was stratified into currently smoking or not smoking at baseline.

** To establish the coronary artery calcium score, deposits of calcium in the LAD were quantified according to the Agatston score. In total, 67 patients were excluded because they had been scanned with a different CT scanner, because of use a deviating CT scan protocol, or because coronary artery stents caused too many artifacts for reliable CAC scoring.

†† Chemotherapy regimens were 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or adriamycin and cyclophosphamide (AC), or taxane-based chemotherapy.

‡‡ The mean dose to the atherosclerotic plaque was calculated for the 163 patients with an atherosclerotic plaque present at baseline.

was significantly higher compared with the nonplaque group, in which 19 patients (2.8%) developed an ACE during follow-up ($P \leq .001$). The 9- and 12-year cumulative incidence of ACEs for patients with an atherosclerotic plaque was 11.1% and 18.9%, respectively. For patients without a LAD atherosclerotic plaque, the 9- and 12-year cumulative incidence was 2.6% and 3.6%, respectively (Figure 1). The 9- and 12-year

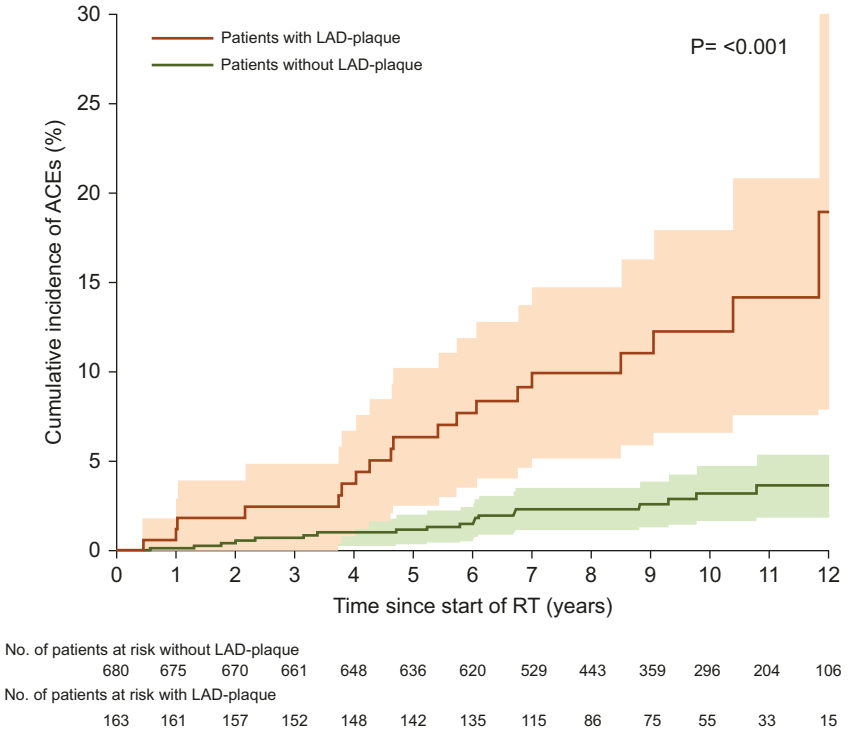

Fig. 1. Cumulative incidence of acute coronary events for patients without an atherosclerotic plaque in the left anterior descending coronary artery (LAD) and patients with an atherosclerotic plaque in the LAD. The light green and orange area indicates the 95% confidence intervals.

cumulative incidence for the total study population was 3.9% and 5.7%, respectively (Figure E3).

The following risk factors were all significantly different between the 2 groups: age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes. Chemotherapy was prescribed more frequently in the group of patients without an atherosclerotic plaque.

More detailed information about the distribution of the MHD, LV-V5, mean LAD dose, and mean dose to the atherosclerotic plaques in the LAD is provided in Figures ES4 to ES7.

Dose-effect relationships

The results of the unadjusted univariable Cox regression analysis between dose and the cumulative incidence of ACEs for patients with and without an atherosclerotic plaque in the LAD are shown in Table 2. In the group of patients with an atherosclerotic plaque (n = 163), the hazard ratio (HR) was 1.116 (95% CI, 0.921-1.353; $P = .263$) for the MHD, 1.014 (95% CI, 0.999-1.030; $P = .076$) for the LV-V5, and 1.029 (95% CI, 1.002-1.057; $P = .034$) for the mean dose to the LAD, respectively. For patients with a plaque, the mean dose to these plaques was significantly associated with the incidence of an ACE (HR, 1.195; 95% CI, 1.041-1.370; $P = .011$), indicating a 19.5% increase in relative risk for an ACE per gray mean dose plaque. Based on these unadjusted univariable models, the cumulative excess risks per gray or percent were calculated for patients with and without an atherosclerotic plaque (Fig. ES8).

For patients without plaques (n = 680), the HR was 1.153 (95% CI, 0.983-1.353; $P = .080$) for the MHD, 1.020 (95% CI, 1.004-1.036; $P = .013$) for the LV-V5, and 1.021 (95% CI, 0.995-1.047; $P = .116$) for the mean dose to the LAD.

Finally, the models were corrected for cardiovascular risk factors: age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes, which were all significantly different between the 2 groups (Table 1). Table 2 shows the results of the unadjusted and adjusted models, and the cumulative excess risk due to RT for patients with and without an atherosclerotic plaque based on the adjusted models are shown in Figure 2. The presented models in Figure 2 are corrected for age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes. Because age is one of the most important predictors of ACEs,[3,4] only age and dose are presented in these graphs.

In the group of patients with an atherosclerotic plaque, the HR was 1.117 (95% CI, 0.902-1.383; $P = .309$) for the MHD and 1.014 (95% CI, 0.997-1.032; $P = .100$) for the LV-V5. The mean LAD dose had a borderline significant effect (HR, 1.028; 95% CI, 0.999-1.057; $P = .055$). For patients with a plaque in the LAD, the mean dose to the plaque was highly associated with the excess risk of an ACE (HR, 1.269; 95% CI, 1.090-1.477; $P = .002$). Because almost all atherosclerotic plaques were located in the proximal part of the LAD, it was important to confirm that there was also no dose-effect relationship between the proximal

Table 2 Unadjusted and adjusted analysis calculated with a Cox regression model between dose or percent and the cumulative incidence of acute coronary events

Variable	HR	95% CI	P*
Patients with an atherosclerotic plaque in the LAD			
Unadjusted model			
Mean heart dose	1.116	0.921-1.353	.263
Adjusted model†			
Mean heart dose	1.117	0.902-1.383	.309
Unadjusted model			
LV-V5	1.014	0.999-1.030	.076
Adjusted model†			
LV-V5	1.014	0.997-1.032	.100
Unadjusted model			
Mean dose, LAD	1.029	1.002-1.057	.034
Adjusted model†			
Mean dose, LAD	1.028	0.999-1.057	.055
Unadjusted model			
Mean dose, plaque	1.195	1.041-1.370	.011
Adjusted model†			
Mean dose, plaque	1.269	1.090-1.477	.002
Patients without an atherosclerotic plaque in the LAD			
Unadjusted model			
Mean heart dose	1.153	0.983-1.353	.080
Adjusted model†			
Mean heart dose	1.161	0.966-1.395	.112
Unadjusted model			
LV-V5	1.020	1.004-1.036	.013
Adjusted model†			
LV-V5	1.021	1.003-1.039	.023
Unadjusted model			
Mean dose, LAD	1.021	0.995-1.047	.116
Adjusted model†			
Mean dose, LAD	1.015	0.986-1.046	.312

The presented models are shown for patients with (n = 163) and without (n = 680) an atherosclerotic plaque in the LAD. The adjusted models were corrected for age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes.

Abbreviations: ACE = acute coronary event; CI = confidence interval; HR = hazard ratio; LAD = left anterior descending coronary artery; LV-V5 = volume (%) of the left ventricle receiving at least 5 Gy.

* *P* value was calculated using univariable or multivariable Cox regression analysis between the variable and the occurrence of an acute coronary event.

† Effect was adjusted for risk factors at baseline (eg, age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes).

part of the LAD and the occurrence of ACEs. Therefore, the analysis was repeated for the mean dose to the proximal, middle, and distal part of the LAD (Table ES1 and Fig. ES9-ES10). All subsections of the LAD had a small effect on the development of an ACE.

Furthermore, we tested the relationship of the maximum dose to the LAD and its atherosclerotic plaque with the cumulative incidence of ACEs. For the maximum dose to the LAD, we found no significant association with ACEs for patients with an atherosclerotic plaque (HR, 1.018; 95% CI, 0.996-1.040; $P = .103$) or without one (HR, 1.003; 95% CI, 0.982-1.025; $P = .758$). We repeated the multivariable Cox regression analysis for the maximum dose to the atherosclerotic plaque and found a significant but almost negligible effect in the multivariable analysis (HR, 1.046; 95% CI, 1.014-1.079; $P = .004$). For the group of patients without a plaque in the LAD, the LV-V5 remained an important predictor (HR, 1.021; 95% CI, 1.003-1.039; $P = .023$).

Discussion

The results of this study suggest that for the group of patients with atherosclerotic plaques in the LAD, the mean dose to these plaques seems more relevant for the development of ACEs than the MHD, LV-V5, mean dose to the LAD, or maximum dose to the LAD and its atherosclerotic plaques. For the group of patients without atherosclerotic plaques, the LV-V5 remains an important predictor of ACEs; this represents most patients with BC.

Recent studies have shown a dose-effect relationship between the MHD and the occurrence of ACEs.[3,4] An increase of approximately 16% was found in the cumulative incidence of ACEs per Gy MHD in the first 9 years after RT. This study showed similar HRs associated with years of additional follow-up (median follow-up, 9.2 years vs 7.6 years) but no significant dose-effect relationship between the MHD and ACEs for patients with and without an atherosclerotic plaque. However, as shown in our previously published study,[4] the LV-V5 was an important predictor of ACEs for patients without an atherosclerotic plaque. Among patients with an atherosclerotic plaque, the MHD, LV-V5, and mean dose to the LAD were nonsignificant predictors of ACEs. However, the HRs were all similar to our previously published results based on the whole group of BC patients; the lack of statistical significance found in this subset analysis is most likely due to a lack of statistical power.

In 2 studies, coronary angiography was performed for women with BC 10 and 12 years after RT.[10,11] In 1 of the studies, 85% of patients with left-sided BC who underwent cardiac catheterization showed coronary stenosis involving the LAD. This was a substantially larger percentage than the expected distribution (46%) of coronary artery disease located in the LAD.[10] In the other study, patients with left-sided BC treated with RT had a significant increase of stenosis in the middle and distal part of the LAD. The risk for more severe stenosis was higher with respect to patients with right-sided BC.[11] However, no information was available concerning the presence of coronary artery stenosis before radiation. In contrast, a study by Darby et al found that the estimated mean LAD dose did not improve prediction of the rate of ACEs during a follow-up period of more than 20 years.[3] These findings are consistent with those of the current study; we found a small and nonsignificant effect of the mean LAD dose for patients with and without an atherosclerotic plaque. These data suggest that radiation exposure to the LAD is not the most important indicator for the development of radiation-induced coronary heart disease for the general population.

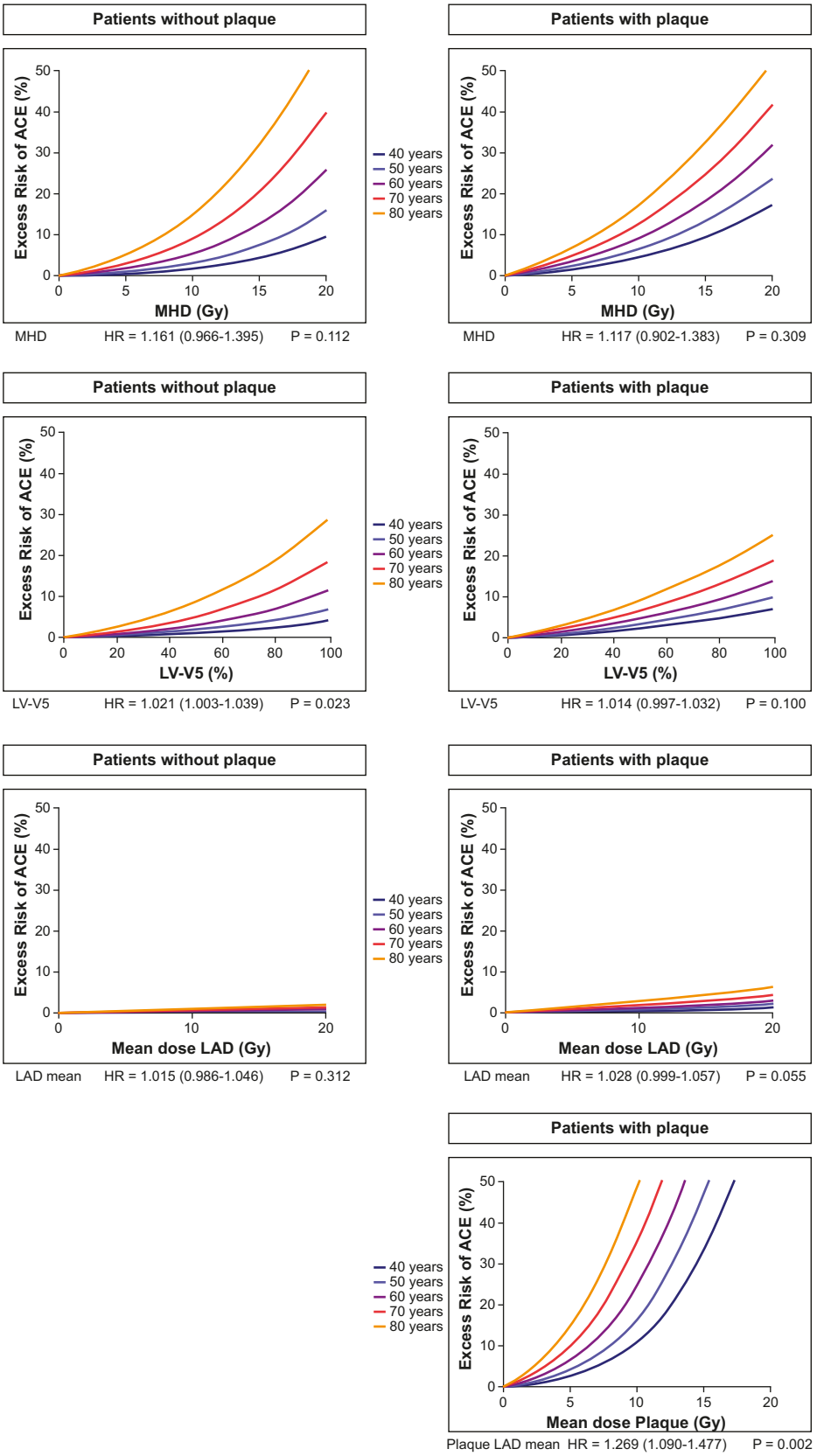

Fig. 2. Excess risk per gray or percent of an acute coronary event, depending on the mean heart dose, volume of the left ventricle receiving ≥5 Gy (LV-V5), mean dose to the left anterior descending coronary artery, and mean dose to its atherosclerotic plaque. The models were analyzed separately for patients with and without an atherosclerotic plaque. The presented models were corrected for age, history of ischemic heart disease, hypertension, hypercholesterolemia, and diabetes; only age and dose are shown.

However, our results suggest that radiation exposure to the "unhealthy" atherosclerotic parts of the LAD is most relevant.

Changes observed in atherosclerosis and in the normal aging process are produced or accelerated by irradiation.[24] After cancer treatment, intimal thickening, lipid deposition, and adventitial fibrosis are found within the vascular system. Possibly, the effects of radiation exposure to "healthy" nonatherosclerotic LAD takes decades to develop, owing to the relatively slow progression of atherosclerosis, and the follow-up time for this study was simply too short. A possible explanation is that the LV-V5 and not the dose to the LAD is more important for the group of patients without an atherosclerotic plaque.

Limited data exist on pre-existing coronary artery atherosclerosis and the effects of treatment over time for oncology patients. One study investigated the longitudinal change of CAC scores among patients with a cancer diagnosis compared with the general population.[25] The researchers found, after adjustment for risk factors, that the progression of pre−existing CAC scores was not statistically different between the 2 groups. However, the relatively low number of participants with cancer limited the power of the analysis, and no information about the cancer treatment was provided.

A limitation of our study is that we investigated calcified plaques based on a Hounsfield unit value of more than 130. Soft plaques with a Hounsfield unit value below 130 were not detected and therefore were not included in the analysis. The literature has shown that soft, lipid−rich plaques, heavily infiltrated by macrophages, are possibly more prone to rupture than calcified plaques.[26,27] Compared with stable collagenous plaques, radiation-related plaques tend to grow, rupture, and lead to a myocardial infarction more frequently.[14,15] However, the effect of radiation to pre-existent soft or calcified plaques is largely unknown.

Another limitation of our study is the relatively small numbers of ACEs. In total, 38 patients developed an ACE during follow-up. To prevent overfitting, the number of candidate predictors in the multivariable analysis was limited, and additional important predictors of ACEs, such as systemic treatment, could not be included. It is important to note, therefore, that the results of this study should only be used for hypothesis generation and that further research is required for validation of this study's hypothesis. Large cohorts involving retrospective and prospective data are currently being collected in subsequent studies such as the BACCARAT prospective cohort study and the MEDIRAD BRACE and MEDIRAD EARLY HEART studies.[28-30] If these large cohorts could validate that pre-existing plaques can be used to select patients at increased risk for radiation-induced ACEs, these high-risk patients could benefit from dose-reducing strategies such as proton irradiation.

Conclusions

In patients with an atherosclerotic plaque, the mean dose to the plaque seems more strongly associated with ACEs than the LV-V5, MHD, and mean dose to the LAD. Furthermore, the LV-V5 remains an important predictor of ACEs for patients without an atherosclerotic plaque.

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