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Radiation related cardiac morbidity

Different manifestation of irradiation induced coronary artery disease detected with coronary computed tomography compared with matched non-irradiated controls

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ABSTRACT

Background and purpose: Patients who received chest irradiation for treatment of a malignancy are at increased risk for the development of coronary artery atherosclerosis. Little is known about the anatomical coronary artery plaque characteristics of irradiation induced coronary artery disease (CAD). This study aimed to evaluate potential differences in the presence, extent, severity, composition and location of CAD in patients treated with mediastinal irradiation compared with non-irradiated controls matched on age, gender and cardiovascular risk factors.

Material and methods: Seventy-nine asymptomatic Hodgkin and non-Hodgkin lymphoma survivors, all treated with mediastinal irradiation with or without chemotherapy, who underwent coronary computed tomography angiography (CTA) to exclude or detect CAD were included. Patients were 1:3 matched with non-irradiated controls ($n = 237$) for age, gender, diabetes, hypertension, hypercholesterolemia, family history of CAD and currently smoking. Mean age at cancer diagnosis was 26 ± 9 years and age at the time of coronary CTA was 45 ± 11 years.

Results: More patients had an abnormal CTA (defined as any coronary artery atherosclerosis): 59% vs. 36% ($P < 0.001$) and significantly more patients had two vessel CAD: 10% vs. 6% and three vessel/left main CAD: 24% vs. 9% compared with controls (overall $P < 0.001$). The maximum stenosis severity among patients was less often <30% (53% vs. 68%) and more often >70% (7% vs. 0%) (overall $P = 0.001$). Patients had more coronary artery plaques in proximal coronary artery segments: left main (17% vs. 6%, $P = 0.004$), proximal left anterior descending artery (30% vs. 16%, $P = 0.004$), proximal right coronary artery (25% vs 10%, $P < 0.001$) and proximal left circumflex artery (14% vs 6%, $P = 0.022$), whereas the number of plaques in non-proximal segments did not differ between groups.

Conclusions: Hodgkin and non-Hodgkin lymphoma survivors treated with mediastinal irradiation with or without chemotherapy showed a higher presence, greater severity, larger extent and more proximally located CAD compared with age, gender and risk factor matched non-irradiated controls. These findings represent features of higher risk CAD and may explain the worse cardiovascular outcome after chest irradiation.

Advances in treatment of patients with cancer have led to improved survival, but have also increased morbidity and mortality due to treatment side effects [1]. Mediastinal irradiation is an effective (part of) treatment for several malignancies but carries increased risk for ischemic and other heart disease [2–4]. Among Hodgkin lymphoma survivors treated with mediastinal irradiation with or without chemotherapy, a 3.6 time increased risk for myocardial infarction has been observed compared with the general population [5]. Moreover, the risk for coronary events is proportional to the irradiation dose. Van Nimwegen et al. observed an increased risk of 7.4% per Gray of mean heart irradiation dose for the development of coronary artery disease (CAD) among 2617 Hodgkin lymphoma survivors [4]. Because of the improving survival of irradiated patients, an increasing number of patients will become at risk for the development of irradiation induced CAD. The European Society of Cardiology states that it appears

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appropriate to screen for CAD after chest irradiation starting 10–15 years after initial cancer therapy [6]. Approaches for early detection of CAD include anatomical assessment (direct visualization of the coronary artery atherosclerosis, which can be performed with coronary computed tomography angiography, CTA) or functional assessment (indirect assessment of CAD by detecting stress-induced myocardial ischemia, as a consequence of coronary artery atherosclerosis, which can be performed by exercise testing, radionuclide perfusion imaging or stress echocardiography) [7,8]. In Hodgkin lymphoma survivors treated with high doses of mediastinal irradiation, coronary CTA, stress echocardiography and radionuclide myocardial perfusion imaging all showed a high prevalence of abnormal findings enabling to initiate medical therapy or percutaneous coronary intervention at an early stage [7,8]. Coronary CTA is specifically suited for detection of CAD at an early stage. Furthermore, it has the unique ability to assess the total coronary artery plaque burden, as well as assessment of the severity, composition and location of the CAD which is prognostically important and clinically relevant [9]. Differences in CAD characteristics may explain the disproportional high coronary event rate in cancer survivors treated with chest irradiation, even at young age, as compared to patients with CAD without cancer therapy. Therefore, the current study aimed to assess the presence, extent, severity, composition and location of CAD detected with coronary CTA in irradiated Hodgkin and non-Hodgkin lymphoma survivors compared with age, gender and cardiovascular risk factor matched non-irradiated controls.

Materials and methods

Patients

In total, 79 patients survived Hodgkin or non-Hodgkin lymphoma and were at least 10 year disease free. All were asymptomatic and underwent mediastinal irradiation as part of their treatment. Patients were treated at the Leiden University Medical Center (LUMC, The Netherlands) between 1980 and 2005. Most patients were treated with either 2D or 3D anterior–posterior-posterior–anterior virtually simulated treatment plans, before the 3D-conformal planning radiotherapy era. Of the 79 patients, radiotherapy volumes included involved fields ($N = 43$, 54%), mantel field (mediastinal and axillary fields, $N = 18$, 23%), subtotal field (mediastinal, axillary, para-aortic and splenic fields, $N = 12$, 15%) or total field (subtotal and pelvic fields, $N = 3$, 4%) and unknown ($N = 3$, 4%). All patients underwent coronary CTA for assessment of CAD as part of a clinical care track evaluating late cardiovascular toxicity. Patients did not have a prior diagnosis of CAD. A subset of the patients was included in the SCAR trial (Screening for Coronary Artery Disease After Mediastinal Irradiation) (NCT01271127) [10]. To assess differences in presence, extent, severity, location and composition of CAD between irradiated patients and non-irradiated controls, patients were matched in a 1:3 fashion based on age (±2 years), gender, diabetes, hypertension, hypercholesterolemia, family history for CAD and smoking status. Matched controls were derived from a large coronary CTA database from the department of cardiology of the LUMC that includes individuals with suspected or known CAD. Patients with an uninterpretable coronary CTA were excluded. Demographical and clinical data were prospectively collected in the departmental electronic information system (EPD-Vision©, LUMC, The Netherlands). The LUMC Institutional Review Board approved this retrospective evaluation of clinically acquired data and waived the need for patient written informed consent.

CT acquisition and image analysis

Patients were scanned using a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems, Japan) or a 320-slice CT scanner (Toshiba Multi-slice Aquilion ONE system, Toshiba Medical Systems, Japan). The patient's heart rate and blood pressure were monitored before the CT acquisition. To maximize image quality, patients with a heart rate exceeding 60 beats per minute (bpm) received 50–150 mg metoprolol and an additional intravenous dose of metoprolol (up to 15 mg) if the heart rate remained >65 bpm during the scout images. Sublingual nitroglycerin (0.4 mg) was administered to induce coronary artery vasodilation. First, a non-contrast scan was acquired for calculation of the coronary artery calcium (CAC) score. Second, coronary CTA was acquired using prospective ECG gating and covering 70–80% of the R-R interval. A broader range of the R-R interval (typically 30–80%) was scanned when the heart rate exceeded 65 bpm to gain more data to allow reconstructions in systolic and diastolic cardiac phases. All scan parameters have been previously published [11].

Images were analyzed using dedicated post-processing software (Vitrea FX 6.5; Vital Images, Minnetonka, Minnesota, USA). The CAC score was calculated using the Agatston algorithm as previously described [12]. Coronary anatomy was assessed in a standardized way by dividing all coronary arteries with a diameter ≥1.5 mm into a 17-segment coronary tree model [13]. Stenosis severity per segment was assessed in accordance with the SCCT guidelines for the interpretation and reporting of coronary CTA: <30%, 30–50%, 50–70%, >70% and occluded [14]. Obstructive CAD was defined as ≥50% stenosis in a coronary artery. After assessing stenosis severity, plaque composition was determined in all diseased coronary artery segments. Plaque composition was classified as calcified (plaques with predominantly calcified tissue), mixed (plaque containing <50% calcified tissue) and non-calcified (plaque containing no calcified tissue). As a measure of overall coronary artery plaque distribution, a segment involvement score was calculated. This score is defined as the total number of coronary artery segments with plaque, irrespective of the degree of stenosis [9]. Furthermore, the segment stenosis score was calculated representing the overall coronary artery plaque severity. Each coronary artery segment was graded (0 to 3) as no plaque to severe plaque based on stenosis severity: <30% or 30–50% = 1, 50–70% = 2 and >70% = 3. The scores of each segment were summed to obtain the segment stenosis score per patient. A case example with calculation of the two scores is demonstrated in Fig. 1.

Statistical analysis

Continuous variables are reported as mean ± standard deviation or median with 25–75% interquartile range (IQR) according to the distribution of the data. Normally distributed variables were compared with the independent-samples *t*-test. Non-normally distributed variables were compared with the Mann–Whitney *U* test. Categorical variables are reported as number and percentage and compared with the chi-square test. First, coronary artery plaque presence, extent, stenosis severity and composition were compared between patients and matched controls. Second, the location of the CAD was compared between the patients and matched controls. Because of the prognostic importance of coronary artery stenosis located in proximal coronary artery segments, the prevalence and severity of coronary artery plaque in the left main, proximal right coronary artery (RCA), proximal left anterior descending artery (LAD) and proximal left circumflex artery (LCX) were compared between the groups. Finally, logistic regression analysis was performed to assess the risk for patients of having several adverse coronary CTA findings. All analyses were performed with

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