Author: Daniëls, Laurien Aletta
Title: Late effects after treatment for Hodgkin lymphoma
Issue Date: 2014-10-14

chapter 3

Screening for coronary artery disease after mediastinal irradiation in Hodgkin lymphoma survivors: phase II study of indication and acceptance

Annals of Oncology 2014; 25(6):1198-203

L.A. Daniëls
A.D.G. Krol
M.A. de Graaf
A.J.H.A. Scholte
M.B. van 't Veer
H. Putter
A. de Roos
M.J. Schalij
C.L. Creutzberg

Abstract

Background
Cardiovascular diseases are the most common nonmalignant cause of death in Hodgkin lymphoma (HL) survivors, especially after mediastinal irradiation. We investigated the role of computed tomographic coronary angiography (CTA) as a screening tool for coronary artery disease (CAD) in asymptomatic HL survivors, and related CTA findings to exercise testing and subsequent interventions.

Patients and methods
Patients were eligible for this phase II study if at least 10 years disease-free and treated with mediastinal radiotherapy. Screening consisted of electrocardiogram, exercise testing and CTA. Primary endpoint was significant CAD (stenosis $>$50%) on CTA. CTA screening was considered to be indicated for testing in a larger population if $\geq$ 6 out of 50 CTA scanned patients (12%) would need revascularization. Screening was evaluated with a questionnaire before and after screening.

Results
Fifty-two patients were included, and 48 patients underwent CTA. Median age was 47 years, time since HL diagnosis 21 years. There were 45 evaluable scans. Significant CAD on CTA was found in 20% (N=9), significantly increased compared with the 7% expected abnormalities (p=0.01, 95% CI 8.3-31.7%). In 11% (N=5) significant stenosis was confirmed at coronary angiography, and revascularization was carried out. Additionally, two patients were treated with optimal medical therapy. Ninety percent of patients were content with screening, regardless whether the CTA showed abnormalities.

Conclusions
Prevalence of significant CAD among HL survivors is high, while asymptomatic even in the presence of life-threatening CAD. This might justify screening by CTA in asymptomatic HL survivors who had mediastinal radiotherapy, but needs to be evaluated in a larger cohort.

Introduction

Over the past 30 years, disease-specific survival in Hodgkin lymphoma (HL) patients has increased dramatically due to improved treatment strategies. However, HL survivors remain at risk of developing late treatment sequelae resulting in increased morbidity and mortality. Cardiovascular diseases (CVD) are the most common non-malignant cause of death in these patients (1). A three- to fourfold increased risk of myocardial infarction due to coronary artery disease (CAD) has been observed, especially in HL survivors who had mediastinal irradiation as monotherapy or in combination with chemotherapy (2, 3). The course of CAD in HL survivors is often asymptomatic, even in the presence of severe stenosis (4). Traditional risk assessment therefore fails to identify HL survivors at high risk for myocardial infarction. More rigorous surveillance in this population seems warranted. The current gold standard for detecting CAD, invasive coronary angiography (CAG), is unsuitable for screening purposes due to risks of complications and mortality. A recent review of studies investigating noninvasive screening techniques for CAD in HL survivors reported disappointing test characteristics of exercise testing, with a reported sensitivity for significant CAD stenosis of only 59%. Moreover, 25% subsequently developed symptomatic CAD within a follow-up duration of 6.5 years (4). Recently, high diagnostic accuracy of screening with computed tomographic coronary angiography (CTA) has been shown in symptomatic patients at intermediate or high risk for CAD (5). A recent study using CTA as a screening tool for CAD among childhood survivors of HL showed a high prevalence of coronary abnormalities (6).

The purpose of this phase II study was to investigate the role of CTA as a screening tool for CAD in asymptomatic HL survivors who underwent mediastinal irradiation as part of their treatment, to relate CTA findings to electrocardiogram (ECG) exercise testing, and to determine the frequency and type of subsequent coronary interventions prompted by CTA. In addition, health-related quality of life (HRQL) and acceptance of screening among patients included in the study was evaluated, both before and after cardiac screening.

Methods

Patients

Long-term HL survivors treated at the departments of Radiation Oncology and Hematology at Leiden University Medical Center (LUMC) were invited to participate. Patients with all stages of HL who were at least 10 years disease-free and had received mediastinal radiotherapy as part of their treatment were eligible. Exclusion criteria were age >60 years; current treatment of CVD other than hypertension, dyslipidemia or minor valve defects; previous CTA in the past 2 years; renal function impairment; known contrast allergy and/or presence of a life-threatening disorder.

Study protocol

This was a single-institution phase II study. The trial protocol was approved by the LUMC Ethics Committee and registered with ClinicalTrials.gov, NCT01271127. After obtaining written informed consent, information on patient and treatment characteristics including radiation treatment fields and dose, and type and dose of (anthracycline-containing) chemotherapy were collected from patient files. Patients were referred to the Cardiology Outpatient Clinic for extensive cardiovascular screening. This included a detailed patient history focusing on specific symptoms and risk factors for CVD, physical examination, fractionated serum cholesterol and glucose testing, resting ECG, echocardiography and symptom-limited exercise ECG testing (7). At a separate visit, cardiac CTA imaging was carried out using a 320-detector row volumetric scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) according to standard clinical practice (8). Patients with a heart rate above 65 beats/min received 50 or 100 mg metoprolol orally 1 h before imaging, unless contraindicated. In addition, sublingual nitroglycerin (0.4 or 0.8 mg sublingual) was administered 5 min before the start of the scan (9). Noncontrast-enhanced and contrast-enhanced scans were carried out. The nonenhanced scans were used to assess the total amount of coronary artery calcium score according to Agatston (10). CTA datasets were evaluated for plaque constitution in a consensus reading by two experienced observers, who were aware of the patients history regarding radiation treatment, but not of any possible current symptoms. Results of CTA were classified as normal (<30% luminal narrowing), nonsignificant CAD (30-50% luminal narrowing) or significant CAD (>50% luminal narrowing).

Results of all examinations and potential indications for further analysis or treatment were discussed during a subsequent visit. If a significant coronary stenosis was observed on CTA, diagnostic coronary angiography was carried out, according to standard LUMC Cardiology protocols.

Assessment of HRQL

Patients were asked to complete three validated HRQL questionnaires at baseline and at completion of the study. The EORTC QLQ C-30 questionnaire measures health-related quality of life (11). The EORTC INFO-25 measures patient satisfaction with regard to received information on treatment (12); and the FAS (fatigue assessment scale) is a rating scale for fatigue and loss of energy (13). An additional short questionnaire of nine items, designed specifically to evaluate acceptance of screening, was added (see appendix Chapter 4).

Study design

Primary endpoint was the presence of significant CAD (> 50% stenosis) on CTA. With an estimated rate of 7% significant coronary disease in asymptomatic healthy individuals (14), and increased relative risk of three in HL survivors (2), we expected to identify significant coronary stenoses in 20-25% of our HL population. A sample size of 50 patients would achieve ≥80% power to detect a threefold relative increase of 7% to 20%, and thus an absolute increased risk of 13%, using a two-sided binominal test with $\alpha \leq 0.05$. With an expected prevalence of significant coronary stenoses of 20%, it is assumed that 10 out of 50 scans will demonstrate significant CAD. Allowing for false-positive scans, we considered CTA screening to be indicated for testing in a larger population if in ≥ 6 patients out of 50 CTA scanned patients (12%) revascularization would be indicated.

Secondary objectives were to determine the frequency and type of subsequent interventions, to compare CTA findings to exercise ECG testing results, to evaluate HRQL and acceptance of screening, and to compare prevalence and location of coronary artery stenoses to CTA findings from an age, sex and risk factor matched control population.

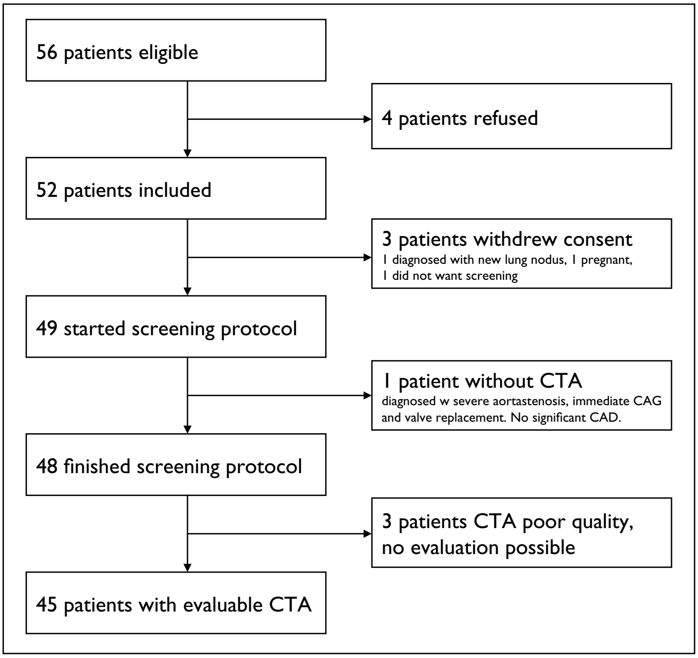

Figure 3.1: CONSORT diagram for CTA analysis

Statistical analysis

All statistical analyses were performed using SPSS statistical software for windows version 20. For the analysis of the primary endpoint all patients with evaluable CTAs were included. Analyses of secondary objectives were done in a descriptive manner. Evaluation of HRQL was done by using EORTC guidelines (15). Prevalence, location and aspect of CAD in our study population were compared to sex, cardiac risk factor and age-matched cases from an ongoing CTA registry at the LUMC Cardiology Department containing CTA results from >1000 patients presenting with chest pain who underwent cardiac evaluation.

Results

Patients were included between January 2011 and March 2012 (Figure 3.1).

Among the 52 included patients, 3 withdrew after signing informed consent. One patient did not undergo CTA due to immediate intervention for severe aortic valve stenosis. The remaining 48 patients completed the screening protocol. Characteristics of the 48 patients finishing the CTA screening protocol are summarized in Table 3.1. Median age was 47 years (range 29-60 years), 60% was female. Thirteen patients (27%) had been treated with radiotherapy as monotherapy, 35 with combined modality treatment. Median dose of mediastinal radiotherapy was 36 Gy (range 24-40 Gy). Radiotherapy volumes most frequently used were involved field in 25 patients, mantle fields (mediastinal and axillary fields) in 11 and subtotal nodal fields (mediastinal, axillary, para-aortic and splenic fields) in 9.

Nine patients received a cumulative anthracycline dose of ≥300 mg/m2 (median dose 360 mg/m2). Most patients had no risk factors for developing CAD; the risk factor most frequently reported was Body Mass Index (BMI) >25, which was present in 19 patients (median BMI 27 kg/m2). Detailed treatment characteristics of patients with abnormal CTA results are described Table 3.2.

CTA results

In total, 48 patients underwent CTA. Due to increased heart rates resistant to β-blocking agents and resulting in motion artefacts on CTA, three scans were not evaluable. Another 12 scans were of suboptimal quality, due to the same problem, but were of sufficient quality for evaluation. In the 45 scans available for assessment, the prevalence rate of significant CAD on CTA was 20% (N=9, p=0.01, 95% CI 8.3 - 31.7%) and thus significantly increased compared with the expected population prevalence rate of 7%. Eight of nine patients with significant CAD on CTA were classified as having a low risk for developing CAD, according to the Framingham Risk Score (16). Eight patients with significant CAD on CTA underwent CAG. In five of these patients significant proximal CAD was confirmed and revascularization procedures carried out, among which two coronary artery bypass grafts for severe left main artery stenosis. The remaining three patients did not need revascularization, but two were started on drug therapy with statins and platelet inhibition (Table 3.3). Accuracy of CTA, defined as the confirmation of abnormalities on CAG resulting in a subsequent intervention was 88% (seven out eight patients who underwent CAG). One patient with possibly significant CAD on CTA refused subsequent CAG, since she had been

Table 3.1: Patient and treatment characteristics

	Number of patients	%
Total	48	
Sex	Number of patients	%
Male	19	40
Female	29	60
Age and time interval	Years	Range
Median age at diagnosis HL	26	(15-37)
Median age at time of study	47	29-60
Median time since diagnosis	21	11-29
Stage (Ann-Arbor)	Number of patients	%
I	8	17
II	34	71
III	4	8
IV	2	4
Treatment	Number of patients	%
Median dose mediastinal radiotherapy (range)	36 (24-40)	
Number of patients receiving combined modality treatment	35	73
Number of patients $>$300 mg/mm2 anthracycline	9	19
Chemotherapy regimes	Number of patients	%
MOPP	5	14
MOPP-ABV	12	34
ABVD	10	29
EBVP	5	14
BEACOPP	3	9
Cardiovascular risk factors	Number of patients	%
Cigarette smoking	4	8
Hypertension	4	8
Diabetes mellitus	0	0
Dyslipidaemia	6	13
Family history positive for myocardial infarction	8	16
Body mass index $>$25	19	40

MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MOPP-ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; EBVP = epirubicin, bleomycin, vinblastine and prednisone; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

Table 3.2: Characteristics of patients with abnormal CTA results

Sex	Current age (yrs)	Time since diagnosis (yrs)	Stage	Chemotherapy	RT fields	Dose mediastinum (Gy)	Risk factors	CAG	Findings CAG	Intervention
F	46	18	2	No	STNI	36	HT, Family	yes	30% stenosis proximal LM	Platelet inhibition Statins
M	55	25	2	3.5 x ABVD	Mantle	36	Smoking, HC, Family	yes	80% stenosis mid RCx total occlusion proximal RCA	Revascularization PCI
F	51	26	2	No	STNI	36	-	no	-	-
M	51	25	2	6 x ABVD	Mantle	40	BMI 28	yes	40% stenosis proximal RCx, RCA	-
F	56	29	3	6 x MOPP	Mantle	35	-	yes	70% stenosis ostium RCA	Revascularization PCI
M	49	21	2	6 x MOPP/ABV	IF	40	-	yes	90% stenosis LM 40-50% stenosis proximal RCA	Revascularization CABG
M	49	29	1	No	Mantle	40	BMI 27	yes	>90% stenosis ostium RCA	Revascularization PCI
M	55	24	1	No	Mantle+PaO	36	-	yes	diffuse arthrosclerosis, no significant stenosis	Platelet inhibition Statins
F	52	18	2	3 x MOPP/ABV	IF	36	-	yes	70-80% stenosis LM	Revascularization CABG

RT = radiotherapy; CAG = coronary angiography; F = female; M = male; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MOPP/ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine; STNI = subtotal nodal irradiation; Mantle = mantle field; IF = involved field; Mantle + PaO = mantle field + para-aortic nodes; HT = hypertension; HC = hypercholesterolemia; Family = family history positive for ischemic heart disease; BMI = body mass index; LM = left main artery; RCx = ramus circumflexis; RCA = right coronary artery; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

diagnosed with breast cancer at the time of CTA. Patients with significant CAD on CTA more often had high calcium scores (75^{th}–100^{th} percentile) than patients who had no severe abnormalities on the CTA scan (55% compared to 17%, Table 3.3).

Matched case-controls

For the nine patients in our study with significant CAD on CTA, the LUMC Cardiology database was searched for matched cases. Due to young age and absence of risk factors in the HL survivors, only a single matching case could be found.

Among the HL patients with CAD on CTA 78% (seven of nine) were treated, either with optimal medical treatment or intervention, while in the matched cases eventually only 22% (two of nine) had significant CAD on CTA necessitating treatment. These small numbers impaired comparison of location or aspect of coronary stenosis.

Exercise ECG testing versus CTA

Results from ECG exercise testing were related to findings on CTA (Figure 3.2). Of the 48 patients that started the screening protocol, 3 were not able to perform an exercise test due to physical impairments. These three patients had no signs of significant CAD on CTA. The remaining 45 patients underwent both ECG exercise testing and CTA. None of the patients had complaints of angina pectoris during the test. Three patients had signs of ischemia on ECG during exercise testing. Presence of significant CAD was found in only one of them. Of the 42 patients with a normal exercise test, 8 had significant CAD on CTA and CAG was carried out in 7. Revascularization was needed in four, and two were started on drug therapy. The two patients with severe left main artery stenosis on CTA and CAG showed no signs of ischemia during the ECG exercise test.

HRQL and acceptance of screening

Forty-seven patients (98%) participated in the HRQL part of this study and completed the first set of questionnaires; 40 completed the second questionnaires, resulting in a response rate of 85%. All patients who underwent CAG returned both questionnaires. Of all patients 90% responded with 'quite a bit' or 'very much' to the question whether

Table 3.3: Patients with coronary artery disease detected at CT Coronary Angiography: calcium scores and subsequent interventions

Patient	FRS	Risk Profile	Exercise testing	Ca score	Percentile	CTA	CAG	Findings CAG	Intervention
F, 46 yr	2%	low	no ischemia	1	50-75	Possible stenosis LM	yes	30% stenosis proximal LM	Platelet inhibition Statins
M, 55 yr	20%	IM	abnormal	438	90-100	Significant stenosis proximal RCx, Total occlusion proximal RCA	yes	80% stenosis mid RCx total occlusion proximal RCA	Revascularization PCI
F, 51 yr	4%	low	no ischemia	69	75-90	Possible stenosis mid RCx	no	-	-
M, 51 yr	7%	low	no ischemia	512	90-100	3-vessel disease	yes	40% stenosis proximal RCx, RCA	-
F, 56 yr	4%	low	no ischemia	466	90-100	50% plaque proximal LAD	yes	70% stenosis ostium RCA	Revascularization PCI
M, 49 yr	7%	low	no ischemia	0	-	60% stenosis ostium LM	yes	90% stenosis LM 40-50% stenosis proximal RCA	Revascularization CABG
M, 49 yr	7%	low	no ischemia	12	50-75	Possible stenosis ostium RCA	yes	>90% stenosis ostium RCA	Revascularization PCI
M, 55 yr	7%	low	no ischemia	1112	90-100	Diffuse extensive arthrosclerosis	yes	diffuse arthrosclerosis, no significant stenoses	Platelet inhibition Statins
F, 52 yr	5%	low	no ischemia	14	50-75	70% stenosis proximal LM	yes	70-80% stenosis LM	Revascularization CABG

F = female; M = male FRS = 10 yr risk of Coronary Heart Disease according to Framingham Risk Score (16); Risk Profile = classification of FRS into low (<10%), intermediate (IM) (10-20%) and high (>20%) categories for 10-year risk of developing CAD (16); Ca score = total score of calcifications in coronary arteries according to the Agatston approach (10); Percentile = reference of calcium score to individuals of the same age and gender; CTA = Computed Tomography Coronary Angiography; CAG = coronary angiography; LM = left main artery; RCx = ramus circumflexus; LAD = left anterior descending; RCA = right coronary artery; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

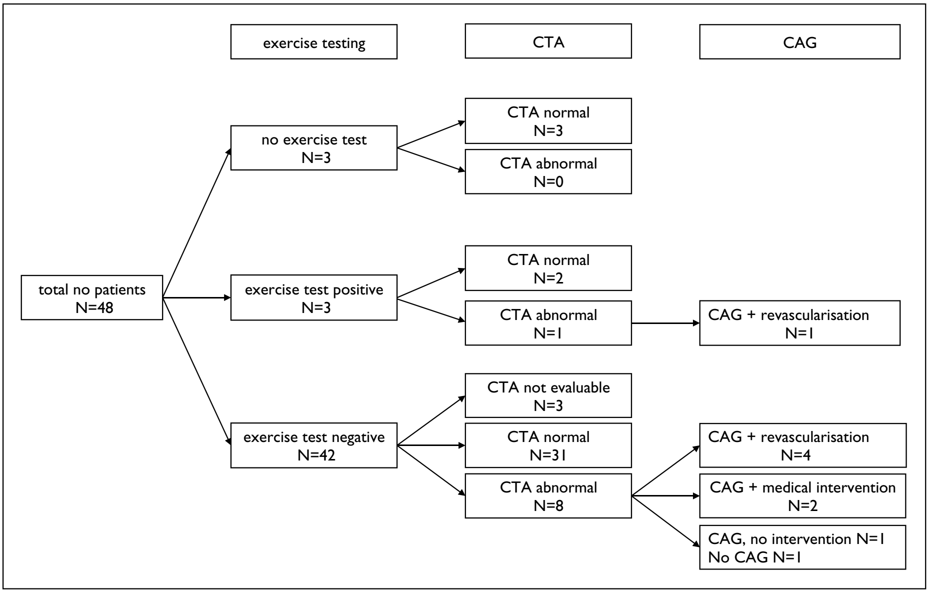

Figure 3.2: Results of exercise ECG testing versus CTA

they were content with participating in the screening study. Visiting the cardiac outpatient clinic and undergoing the CTA was perceived cumbersome by 10% and 20% respectively.

The emphasis that was placed on the possible cardiac effects of treatment of HL was perceived as bothersome by 25%. Full analysis of HRQL will be described in a separate publication.

Discussion

This phase II study investigated the role of CTA as a screening modality for CAD in asymptomatic HL survivors. We detected a 20% prevalence rate of significant ostial or proximal coronary artery stenosis on CTA, the majority of which was confirmed with CAG. Another 22% (N=10) of the study population had an abnormal CTA, with nonsignificant stenosis (30-50%) in the proximal coronary arteries.

Prevalence of CAD on CTA was high, especially considering the fact that almost all patients were categorized as having a low risk for developing CAD, based on young age and absence of risk factors such as smoking or dyslipidemia. Comparing the HL patients to matched cases proved to be difficult, which underlines the fact that HL survivors do not fit the usual high-risk cardiac profile. Only a small proportion of the HL survivors had received a cardiotoxic cumulative dose of chemotherapy, suggesting that previous radiation treatment may be the most probable cause of CAD. The prevalence of coronary stenosis found in this study is likely to be an underestimation of the true occurrence of CVD, since patients with already apparent CAD were ineligible.

In our study, 5 of the 45 evaluable patients (11%), close to the predefined 12%, underwent revascularization procedures. Another two were treated with optimal medical therapy, resulting in a prevalence rate of patients with severe abnormalities needing interventions of 16% (7 of 45). One patient did not complete screening due to immediate treatment of severe aortic valve stenosis.

The potential role of CTA as a screening tool for CAD in asymptomatic HL survivors was tested in two other studies. In a small pilot study including nine patients with a treatment history of mediastinal radiotherapy and a median follow-up duration of 26 years, Rademaker *et al.* found five patients with stenoses >50%, of whom 2 were subjected to CAG and required revascularization. However, in this study most patients had additional risk factors for developing CAD (17). Kupeli screened 119 childhood HL survivors of whom 50% had received mediastinal radiotherapy (median dose 27.5 Gy) after a relatively short median follow-up period of 10 years. Abnormalities on CTA were found in 16%, but only one patient underwent subsequent CAG (6). Although the number of patients in our pilot study is limited, one of the strengths is that in almost all patients with significant stenosis on CTA CAG was carried out to confirm CTA results.

Our study compared different types of noninvasive screening. Only one patient with significant CAD was accurately identified by ECG exercise testing, and none of the participating patients reported symptoms, not even in the presence of severe CAD. These observations confirm the limited value of screening by means of ECG exercise testing in this setting as reported in the literature (2).

Considering these results, and with the knowledge that it has been demonstrated that the predictive value of a negative CTA is high for excluding CAD and correlates with a low risk of cardiac death in the near future (18), it seems justified to conclude that CTA is an effective, and possibly the most suitable noninvasive screening modality for CAD in asymptomatic HL survivors.

CTA screening and cardiac intervention in this population might be advisable, provided that treatment that improves outcome for those with screen-detected abnormalities is available. Survival benefit of cardiac interventions has been demonstrated in high risk symptomatic cardiac patients (19). The CASS study also showed a 30% increase in overall survival in asymptomatic patients treated for proximal left CAD (20). In our patients, all significant stenosis were located in the ostium or proximal in the coronary arteries, resulting in a large cardiac area at risk at the event of occlusion.

Screening and cardiac intervention in asymptomatic HL survivors might therefore also be indicated, but this should be evaluated in larger cohort studies, as it is unlikely that randomized trials will be feasible in this setting. Our study showed that acceptance of screening was high. Regardless whether CTA showed abnormalities or not, 90% was content with the screening study and with being informed on the risk of late cardiac events. In view of the broad acceptance of screening and the high rate of CAD stenoses found in this phase II study, a nationwide study to establish the role of CTA-based cardiac screening in a large population of asymptomatic HL survivors treated with mediastinal radiotherapy should be considered. This could also provide more clarity on timing and frequency of screening, costs of screening and possible effects of screening on HRQL. Positive findings of screening should also be balanced against possible disadvantages such as additional radiation exposure and the risk of complications due to invasive diagnostic procedures.

At LUMC β-blockers are given prior to CTA imaging to optimize image quality. However, a remarkably large proportion of the participants (31%) had elevated heart rates unresponsive to β-blocking agents. This led to non-evaluable CTA scans in three patients, and suboptimal quality images in another 12 patients. Further research on the pathophysiology of this tachycardia will be conducted.

In conclusion, prevalence of severe CAD in asymptomatic long-term HL survivors treated with mediastinal irradiation is significantly increased, and very often asymptomatic, even in the presence of a severe proximal stenosis. This might justify screening by CTA to reduce the risk of life-threatening cardiac events in this population, but the role of CTA-based cardiac screening needs to be evaluated in larger cohort studies.

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