Clinical Investigation: Lymphoma and Leukemia

# Prospective Coronary Heart Disease Screening in Asymptomatic Hodgkin Lymphoma Patients Using Coronary Computed Tomography Angiography: Results and Risk Factor Analysis

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## Summary

Using coronary CT angiography (CCTA), coronary artery abnormalities were demonstrated in 26% of patients. Within the first 5 years after treatment, 15% of patients already exhibited CCTA abnormalities. Multivariate analyses evinced that conventional risk factors, radiation dose to the coronary artery origins, and leukocyte telomere length were

**Purpose:** To prospectively investigate the coronary artery status using coronary CT angiography (CCTA) in patients with Hodgkin lymphoma treated with combined modalities and mediastinal irradiation.

**Methods and Materials:** All consecutive asymptomatic patients with Hodgkin lymphoma entered the study during follow-up, from August 2007 to May 2012. Coronary CT angiography was performed, and risk factors were recorded along with leukocyte telomere length (LTL) measurements.

**Results:** One hundred seventy-nine patients entered the 5-year study. The median follow-up was 11.6 years (range, 2.1-40.2 years), and the median interval between treatment and the CCTA was 9.5 years (range, 0.5-40 years). Coronary artery abnormalities were demonstrated in 46 patients (26%). Coronary CT angiography abnormalities were detected in nearly 15% of the patients within the first 5 years after treatment. A significant increase (34%) occurred 10 years after treatment ($P=.05$). Stenoses were mostly nonostial. Severe stenoses were observed in 12 (6.7%) of the patients, entailing surgery with either angioplasty with stent placement or bypass grafting in 10 of

independent prognostic factors. The findings suggest that CCTA can identify asymptomatic individuals at risk of acute coronary artery disease.

them (5.5%). A multivariate analysis demonstrated that age at treatment, hypertension, and hypercholesterolemia, as well as radiation dose to the coronary artery origins, were prognostic factors. In the group of patients with LTL measurements, hypertension and LTL were the only independent risk factors.

**Conclusions:** The findings suggest that CCTA can identify asymptomatic individuals at risk of acute coronary artery disease who might require either preventive or curative measures. Conventional risk factors and the radiation dose to coronary artery origins were independent prognostic factors. The prognostic value of LTL needs further investigation. © 2014 Elsevier Inc.

## Introduction

With extended follow-up beyond 10 years, late mortality in Hodgkin lymphoma patients is predominantly due to non−cancer-related causes, such as second malignancies and cardiovascular events (1-6). Cardiovascular events are mostly represented by coronary artery disease (CAD) with high relative risks (RRs) (1.6-7.8) (3, 4, 7, 8). Multifarious risk factors have been implicated in the development of CAD in Hodgkin lymphoma patients, some related to patient characteristics (such as hypertension, hypercholesterolemia) and others ascribed to radiation treatments (1-8) and/or chemotherapy (7-10). Consequently, reliable cardiac screening in asymptomatic Hodgkin lymphoma survivors might help improve long-term survival. Coronary CT angiography (CCTA) has a high negative predictive value for detecting coronary disease and high diagnostic accuracy in the detection of significant CAD and its severity compared with conventional angiography (11-13). In our study, CCTA was prospectively performed in a large cohort of asymptomatic Hodgkin lymphoma patients treated with combined-modality therapies, including mediastinal irradiation. Conventional and less-conventional risk factors associated with an increased risk of coronary events, such as plasma C-reactive protein levels (14-16), periodontitis (17), and leukocyte telomere length (LTL) (18-21), were assessed in multivariate analyses.

## Methods and Materials

### Patient population

Two hundred one consecutive asymptomatic patients without a prior history of CAD were informed about cardiovascular health risks due to treatments they had received. They were offered screening by CCTA and were notified about the small radiation exposure resulting from the screening procedure (4.5 mSv [±2]). One hundred seventy-nine patients (89%) agreed to enter the study. Risk factors were assessed (body mass index, hypertension, smoking, physical activity according to published guidelines [22], and periodontal disease [23]). Screening for hypertension and hypercholesterolemia was performed during the regular follow-up visits before CCTA. Patients who agreed to participate in the

telomere analysis study signed an informed consent form. The Hematology Committee (Institut Gustave Roussy, Villejuif, France) reviewed and approved the study in accordance with local ethics. Because radiation-associated CAD is characterized by a high prevalence of left main and right coronary artery ostial stenoses (24), all radiation treatment charts or computerized records were reviewed, and radiation doses were estimated according to isodose curves encompassing the area of the coronary artery origins (CAOs) (25). Their radiobiological equivalent (26) was also determined. Major cardiovascular events during follow-up were recorded.

### Study protocol

Coronary CT angiography was performed on patients using a dual-source CT scanner (Somatom Definition Flash, Siemens AG, Forchheim, Germany). Electrocardiogram (ECG)-gated dual-source CT was performed in sequential prospective mode centered on either the mid-diastolic (70% of the RR interval on ECG) or end-systolic phase (40% of the RR). All coronary CCTA studies were performed with 1 mL/kg body weight of intravenous contrast material (iopromide; Bayer Schering Pharma, Berlin, Germany) at 4-6 mL/s. A gantry rotation time of 300 ms was selected to achieve temporal resolution of 75 ms for each slice. The mean radiation dose delivered during the CCTA procedure was 4.5 mSv (±2). All imaging data were reviewed by 2 experienced radiologists.

### LTL analysis

Peripheral blood samples were obtained before CCTA. Whole blood was added to the culture medium with phytohemagglutinin M (GIBCO/BRL, Grand Island, NY) for 48 hours. Blood was incubated at 37°C for 2 hours in the presence of colcemid (0.1 g/mL) before harvesting. Slides were prepared after standard methanol/acetic (3:1, vol/vol) fixation. They were stored at −20°C until use. Leukocyte telomere length was measured in peripheral blood lymphocytes using the quantitative fluorescence in situ hybridization (Q-FISH) technique with a Cy-3−labeled peptide nuclear acid probe specific for (TTAGGG) PNAGENE, Daejon, South Korea. Quantitative image acquisition and analysis were performed using MetaCyte software (version 3.9.1;