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## Risks and diagnosis of coronary artery disease in Hodgkin lymphoma survivors

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### Abstract

Higher mortality rates are reported because of cardiovascular diseases in individuals living in industrialized areas of the World. In cancer patients, cardiotoxic chemotherapeutic agents and/or mediastinal radiotherapy are additional risk factors for the development of coronary artery disease. An improved survival rate for patients with Hodgkin lymphoma was reported in recent decades. Determining and handling the long-term effects of cancer treatment have become more important nowadays, parallel to the good results reached in survival rates. Mediastinal radiotherapy and cardiotoxic chemotherapeutic agents are routinely used to treat Hodgkin lymphoma but are commonly associated with a variety of cardiovascular complications. Drugs used in cancer treatment and radiotherapy may cause deleterious effects on contractile capacity and conduction system of the heart. Approximately ten years after the completion of all therapies, the cardiovascular disease risk peaks in patients who survived from Hodgkin lymphoma. The value of coronary computed tomography angiography as a diagnostic tool in determining coronary artery disease as early as possible is underlined in this review, in patients who are in remission and carry the risk of coronary artery disease probably because of

chemo/radiotherapy used in their treatment. Survivors of Hodgkin lymphoma especially treated with combined chemoradiotherapy at younger ages are candidates for coronary computed tomography angiography.

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**Key words:** Coronary artery disease; Hodgkin lymphoma; Computed tomography angiography; Cardiotoxicity; Survivors

**Core tip:** With substantial increase in survival rates from cancer, late adverse effects of cancer therapy have become extremely important. Mediastinal radiotherapy and cardiotoxic chemotherapeutic agents are routinely used to treat Hodgkin lymphoma (HL) but are commonly associated with a variety of cardiovascular complications including coronary artery disease (CAD). For surviving individuals after HL treatment, coronary computed tomography angiography is a non-invasive and useful method in detecting CAD at an early stage. Survivors of HL especially treated with combined chemoradiotherapy at young ages, who carry the risk of CAD development are candidates for coronary computed tomography angiography.

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### INTRODUCTION

Surviving individuals after treatment of malignant diseases have markedly increased in last decades probably because of advanced diagnostic abilities and effective cancer treatment. Long-term unintended effects of aggressive treatments, unfortunately have emerged as a

serious problem at the same time. The adverse effects on heart are among the deadliest effects having high rate of morbidity and mortality. Cardiotoxic chemotherapeutic agents, such as doxorubicin, daunorubicin and epirubicin can decrease the cardiac functioning and contractility of myocardium and the signs of malfunction may even emerge many years after cessation of cancer treatment<sup>[1-5]</sup>. The degree of cardiac dysfunction depends basically on cumulative drug doses of anthracyclines<sup>[6-11]</sup>. Mediastinal radiotherapy delivered at the same time with cardiotoxic antineoplastic drugs can also affect the normal functioning of the heart in that population<sup>[12,13]</sup>. Screening these individuals for treatment related cardiac toxicity, diagnosing and treating them as early as possible are cornerstones of proper management of cardiovascular disorders. Therefore, screening of cardiac functions of these individuals after cessation of cancer treatment is particularly important and the principles for the following-up of these patients have been published<sup>[14]</sup>.

Some researchers have reported higher relative risks of myocardial infarction mortality in patients treated at younger ages than in patients treated at older ages and in men than in women<sup>[15-19]</sup>. Other researchers have reported valvular dysfunction, carotid, subclavian and coronary artery disease and even fatality from cardiac infarction at early childhood after radiation therapy for the treatment of Hodgkin lymphoma (HL)<sup>[20-23]</sup>. In contrast to numerous papers dealing with cardiac functions in cancer survivors, articles investigating the status of heart and its vasculature in survivors of HL treated in pediatric age group are scarce<sup>[11-13,24]</sup>.

## CORONARY HEART DISEASE

In industrialized Western countries, coronary heart disease is among the leading causes of mortality<sup>[25,26]</sup>. Coronary artery disease (CAD) is diagnosed more often in middle-aged males and it is also one of the major causes of mortality in women after menopause<sup>[27]</sup>. Advanced biological age, hypertension, increased body-mass index, hyperlipidemia, diabetes mellitus, smoking or use of tobacco products, and presence of CAD among the family members are among the traditional risk factors for CAD<sup>[28]</sup>. Researchers are trying to find out genes that create predisposition to CAD<sup>[29-31]</sup>. Besides these, cardiotoxic chemotherapeutic agents and/or mediastinal radiotherapy are additional risk factors for cancer survivors.

## RISK FACTORS IN PATIENTS WITH HODGKIN LYMPHOMA

### *Hodgkin lymphoma*

In developed countries, lymphomas are the third most frequent tumors among the pediatric cancers following leukemias and central nervous system tumors. In contrast, in our country and most of the developing parts of the World lymphomas just follow the leukemias in frequency<sup>[32]</sup>. With advanced diagnostic and therapeutic fa-

cilities the survival rates in low and high risk patients with HL increased to 95% and 90% respectively<sup>[33,34]</sup>. Similarly, improved results after HL treatment were also published in articles from Turkey in recent years<sup>[35,36]</sup>. To diagnose earlier and proper treatment of long-term unwanted effects have become one of the main issues in practice of both Pediatric and Medical Oncology parallel to the good results taken in cancer treatment. The frequency of cardiovascular disease peaks generally five to ten years after the completion of HL treatment<sup>[35,36]</sup>.

### *Treatment toxicity in HL*

In HL combined chemotherapy with low dose involved field radiotherapy (1500-2500 cGy) is the preferred treatment. The mostly used chemotherapeutic regimens in HL are mechlorethamine, vincristine, prednisone and procarbazine (MOPP), cyclophosphamide, vincristine, prednisone and procarbazine (COPP), doxorubicin, bleomycin, vinblastine, dacarbazine (DBVD), OPPA (vincristine, procarbazine, prednisone, adriamycin), and MOPP/DBVD alternating protocols<sup>[33,34]</sup>. Among the acute side effects of multiagent chemotherapy protocols nausea and vomiting are the leading ones. Many chemotherapy schemes produce bone marrow suppression and reversible alopecia. Bleomycine-related pulmonary toxicity, vincristine-related neurotoxicity, doxorubicin-related cardiotoxicity are the other side effects of chemotherapy. Radiation pneumonitis, pulmonary fibrosis, spontaneous pneumothorax, abnormalities in growing soft tissues and bones, cardiovascular, and endocrine abnormalities constitute the late effects of treatment. Second malignant neoplasms, especially ALL, are also among the late effects of therapy<sup>[33,34,37-39]</sup>.

Antineoplastic drugs, especially anthracyclines and mediastinal radiotherapy can cause decrease in cardiac contractility, heart insufficiency, pericardial effusion, constrictive pericarditis, coronary artery disease, myocardial infarction, and arrhythmias<sup>[15-19,40]</sup>. Vascular narrowing and cerebrovascular accidents are also among the late complications. Late subclinical cardiovascular side effects are apparent especially in patients 30 to 50 years of age<sup>[37]</sup>. The most common chemotherapeutic agents implicated in the development of cardiovascular complications include the anthracyclines, alkylating agents, and vinca alkaloids<sup>[41,42]</sup>. Alkylating agents such as cyclophosphamide may exacerbate anthracycline or radiation induced cardiac injury. In adults, the frequency of congestive heart failure increases with the cumulative doxorubicin doses greater than 550 mg/m<sup>2</sup><sup>[37]</sup>. Mediastinal radiation and other chemotherapeutic drugs are thought to lower the threshold. Since then, all patients treated with anthracycline-containing protocols and mediastinal radiotherapy must be followed up for cardiac injury.

### *Effect of radiation on vessels*

In the treatment of HL, anthracyclines and delivering irradiation to the nodal areas affected are routinely administered. Although not more often, deaths because of myocardial infarction at early ages after HL treatment

were reported<sup>[20-23]</sup>. It is impossible to find out exact figures in literature for the frequency of heart diseases in HL survivors. Radiation arteritis may occur as a result of the previous radiation therapy<sup>[43]</sup>. Arteries of young children are more susceptible than those in adults. Stenosis and occlusion can be detected angiographically in arteries in the area of radiation. Additionally computed tomography angiography (CTA) can show arterial wall thickening and radiation effects in other soft tissues.

The effects of radiation in tissues received radiation can be classified into a few groups: occurring in epithelial and parenchymal organs, in blood vessels and in stroma<sup>[43]</sup>. The vessels having the shortest diameter are the most radiosensitive ones. The reason behind this sensitivity is mostly arising from vulnerable character of endothelium layering the vessels. The changes of radiation in tissues are best studied and documented in animal trials and include irregularity of cytoplasm with the formation of pseudopodia or swelling of cytoplasm often obstructing the lumen, detachment of endothelial cells from the basal lamina, cell pyknosis, rupture of plasma membrane, thrombosis, and rupture of the capillary wall<sup>[44]</sup>.

Arteritis occurs basically in vessel wall and inflammation progresses to thickening in arterial wall resembling the process of atherosclerosis<sup>[45]</sup>. Foam cell plaques in medium and small arteries are suggestive of irradiation. Recent studies confirm that acute vasculitis can be induced by ionizing radiation. Some researchers determined acute vasculitis in small arteries next to coronary arteries or iliac arteries exposed to local radiation therapy. The estimated doses received at the sites of vasculitis varies between 600 and 4000 cGy. Large arteries are less often affected from radiation because of their large lumen and thick wall. Some experimental evidence indicates that arterial perforations may occur due to high dose irradiation<sup>[43]</sup>.

### **HL and CAD**

Heart diseases are among the frequently seen long-term effects of chemo/radiotherapy used in HL treatment. Mediastinal radiotherapy and cardiotoxic chemotherapeutic agents are commonly associated with a variety of cardiovascular complications including CAD. The mechanism of injury is multifactorial and likely involves endothelial damage of the coronary arteries and secretion of multiple inflammatory and profibrotic cytokines<sup>[46-48]</sup>. Heidenreich *et al*<sup>[23]</sup> have reported unexpected early deaths from myocardial infarction at young ages after HL<sup>[21-23]</sup>.

Taken into consideration the relation between the degree of HL treatment and treatment related risks on heart, studies conducted with the aim of giving smaller doses of radiotherapy and lower doses or shortened duration of cardiotoxic agents can limit heart toxicity. Monitoring the patients for classical and generally accepted risk factors for CAD is another important method in lowering the incidence of heart diseases in HL survivors. Rademaker *et al*<sup>[13]</sup> reported that coronary CTA and calcium scores are useful methods for the evaluation of irradiation-related CAD in their nine patient series. In a recent study, we investigated CAD by using CTA in 119

HL survivors treated at the pediatric age group<sup>[12]</sup>. Hodgkin lymphoma survivors who are in remission at least 2 years after cessation of treatment were investigated. They were questioned about the coronary artery risk factors. Complete blood count, general biochemistry, lipid profile, cardiac troponin-T (cTT) and creatinine kinase myocardial band have been studied. Additionally electrocardiogram (ECG), telecardiography, echocardiography, and coronary CTA were undertaken in all patients. Using a multiplanar reformat, intensity projection, and volume rendering reformat techniques, CTA images were reviewed and mediastinal and cardiac vascular abnormalities were investigated. In 19 (16%) of the patients we determined coronary artery abnormalities. We found statistically significant relation between radiation therapy delivered to the mediastinum and development of an abnormality in coronaries. Probability of developing a coronary abnormality was 6 to 8 times higher in group of patients receiving mediastinal radiotherapy more than 2000 cGy in comparison with the other group receiving radiotherapy less than 2000 cGy by multivariate analysis ( $P = 0.009$ )<sup>[12]</sup>. This study confirms the detrimental late effects of mediastinal radiotherapy on coronary arteries of growing children.

## **DIAGNOSIS OF CARDIOVASCULAR DISEASES AFTER TREATMENT OF HODGKIN LYMPHOMA**

### **Screening for cardiovascular complications**

Screening the long-term survivors of a malignant disease for chemo/radiotherapy related toxicity on heart and managing the abnormalities as early as possible are obviously vital strategies in good management of cardiovascular complications. For this reason, cardiac monitoring of surviving patients after completion of treatment is an obligation.

It is ideal to find out minimally invasive and accurate methods of diagnosis to describe cardiac toxicity similar to other late-effect studies. Currently, most of the centers use echocardiography (ECHO) for periodic follow-up of the heart condition. cTT, an appropriate serological marker to suspect from damage in myocardium was suggested for earlier detection of anthracycline related toxicity after animal studies<sup>[49]</sup>. However, no elevation of serum cTT after cessation of adriamycin was reported, although insignificant increases were scored in individuals receiving adriamycin<sup>[50]</sup>. Kismet *et al*<sup>[11]</sup> have found no correlation between serum cTT values, cumulative dose of adriamycin, and systolic or diastolic functions of the heart and concluded that screening with ECHO is more appropriate than cTT for determining subclinical cardiotoxicity.

Echocardiography is the most commonly used diagnostic facility to follow cardiac functions of cancer survivors<sup>[1]</sup>. The traditional approach of screening cardiac toxicity comprises a baseline examination before the start of the cardiotoxic chemotherapy and serial measurements of contractile capacity of the heart (*e.g.*, ejection frac-

tion and fractional shortening) during the course of the treatment. However, the measurement of only ejection fraction as an indicator of left ventricular (LV) function is not reliable to determine subclinical disorders of myocardium<sup>[51,52]</sup>. Additionally, conventional Doppler ECHO has some limitations, basically because its dependence on loading conditions, and frequently has negative influence on the interpretation of the findings.

Tissue doppler imaging (TDI) is recently used commonly to evaluate the velocity of myocardial segments with the use of Doppler effect. TDI is superior to traditional Doppler studies in that it can overcome the dependence of loading and detect the abnormalities in LV. This new technique can be employed in evaluation of LV functioning in part or in whole. TDI has some advantages on conventional Doppler ECHO in the evaluation of global or regional diastolic functional capacity of LV<sup>[53]</sup>. Alehan *et al*<sup>[24]</sup> showed that subtle systolic and diastolic malfunction occurs in long-term survivors of HL by using TDI. Survivors treated with anthracycline based chemotherapy and/or mediastinal radiotherapy may suffer from heart toxicity many years after the cessation of treatment. Malfunction in cardiac systole generally follows the dysfunction in cardiac diastole and prophylactic administration of medications such as angiotensin converting enzyme inhibitors can help preventing the deterioration of heart damage. Obviously, more investigation is necessary to find out accurate strategy for monitoring heart toxicity, but it seems at least today, serial examinations of contractile capacity with TDI in individuals who are in remission after HL treatment can help determining patients under risk of cardiac disorders<sup>[24]</sup>.

### Screening for coronary artery disease with CTA in survivors of Hodgkin lymphoma

CTA employs X-ray to screen blood flow in vasculature in whole body<sup>[54]</sup>. X-ray bundles are scattered from a spinning device into the body part which is examined, and they form cross-sectional images that are collected by the computer to give a 3D Picture of the study region. Compared to catheter angiography, the gold standard procedure for evaluation of arteries, involving placement of a catheter and injection of some amounts of contrasted medium into a large vessel, CTA is a minimally invasive procedure. Major and minor complications can be seen in conventional angiography<sup>[55]</sup>. Contrast material is injected into a small vein in CTA, and for most of the patients hospitalization is not necessary. Apart from cost advantage compared to conventional angiography CTA provides information about the vascular wall and soft tissues besides vessel lumen, helps determining the pathologic vessels and additional extra vascular abnormalities in advance<sup>[12,13,56]</sup>.

In the cardiac CT, predicted radiation exposure is 2-2.5 Rem and this is higher than 1.5-2 Rem that is exposed in diagnostic pediatric cardiac catheterization<sup>[54]</sup>. With contemporary modern detectors, the exposure can be decreased by using the ECG dose modulation technique by using higher X-ray doses to evaluate coronary arteries in

diastolic phases and lowered doses in systolic phases<sup>[21]</sup>. In normal coronaries, it is unusual to find calcification in an arterial wall. CTA is also sensitive in detecting calcium in arterial wall<sup>[13]</sup>. The increase in calcium scores can be halted with the use of hypolipidemic drugs in patients with high calcium scores in their coronaries<sup>[57]</sup>. A conventional angiography, however, cannot be indicated solely based on coronary calcium scoring due to its low specificity<sup>[55]</sup>. In the presence of massive coronary calcification, a CTA cannot show the thickening in the vessels because of signal changes<sup>[54]</sup>.

Although the CTA has found a place of application in many fields and clinical situations<sup>[58-61]</sup> it currently has some limitations. Blocked blood vessels make difficult the interpretation of the images<sup>[55]</sup>. The CTA is not yet reliable for visualization of small, vessels in rapidly moving organs. CTA images can be blurred because of movements during the examination or because of the heart that is not beating properly. High-density objects such as metal clips, stents, and calcified plaques prevent the proper visualization of the neighboring tissues by the attenuation they created<sup>[55]</sup>. The dose of radiation exposed during the examination is also a limiting parameter. With a 64-detector computerized tomography, the dose of radiation given to the patients is approximately 6.5 to 15 mSv and this is much more than that used in conventional angiography<sup>[54]</sup>. The examination brings some risks such as allergic reaction to the contrast material and it must not be performed in renal disease, severe diabetes, pregnant or breastfeeding women.

The above mentioned study is the unique study in which CTA was used for determination of abnormalities in coronary arteries in HL survivors treated in childhood<sup>[12]</sup>. The capability of CTA in early detection of CAD was shown for the first time in this patient population. Based on our findings we concluded that individuals at the age of 17-28 years, treated in childhood for HL and carry the risk of CAD and specifically treated with radiation therapy into the mediastinum, are candidates for coronary CTA.

## CONCLUSION

Serial follow-up including screening for valvular disease with TDI and coronary artery disease with CTA and coronary artery calcium scoring, must be applied to the survivors of HL who have been treated with anthracycline including regimens and/or mediastinal radiotherapy like a great majority of the patients with HL.

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