



Cardiotoxicity After the Lymphoma

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SUMMARY

Radiotherapy (RT) is the cornerstone component of the current successful treatment of Hodgkin lymphoma (HL). Although RT has been used alone to cure in most patients in decades, combined modality regimens are preferred in most HL patients currently, besides early-stage lymphocyte predominance HL and for selected patients with classical HL who have contraindications to chemotherapy. Although classic RT fields, doses, and techniques have fundamentally changed over the years, the heart is still an organ at risk, and patients with radiation-induced cardiovascular complications are increased in the long term. In this paper, we aimed to review literature about radiation-induced cardiotoxicity in lymphoma patients treated with mediastinal RT.

Keywords: Cardiotoxicity; Hodgkin Lymphoma (HL); radiotherapy.

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Introduction

A significant proportion of patients diagnosed with malignancy receive radiotherapy (RT) as an indispensable part of achieving long-term survival, especially in patients with Hodgkin lymphoma (HL). The number of cancer survivors after any treatment is increasing as a result of improved treatments and technological development. However, the proportion of patients with radiation-induced complications is being increased in the long term. Cardiovascular complications are probably one of the utmost importance.[1,2]

The association between RT for HL and cardiotoxicity has been reported almost 50 years ago as a case report. Then, authors from Stanford University have reported that the risk is related to mediastinal doses. [3-5] Radiation-induced heart disease develops slowly. Although no threshold dose of RT has been documented, the authors showed a clear dose-response relationship between the developments of cardiovascular toxicity.[6-8] At the end of 9 years median follow-up time, the cardiovascular complication rate is presented

as 11.6% in patients treated because of HL. The most common complications are presented as coronary artery disease (CAD) (19%), arrhythmia (16%), heart failure (12%), heart valve disease (HVD) (11%), and pericardial disease (5%).[9] Dose reduction, RT field, and volume reduction, and employment of modern RT technology are strategies for reducing heart dose. As a result of these strategies, the risk decreased substantially with decreasing mean heart dose. However, there is no clear threshold dose for the zero cardiac risks. Based on the literature, routine measurement of cardiac biomarkers is not recommended routinely in patients treated with RT.

In this paper, we aimed to review literature about cardiotoxicity in lymphoma patients treated with mediastinal RT.

Radiation-induced Heart and Vascular Disease

The differential diagnoses according to the type of tissue affected by the radiation are presented in Table 1.[10] One of the most important developments in RT overtime

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Table 1 Affected cardiovascular tissues after radiotherapy and occurred diseases[10]

Affected tissue	Occurred disease
Pericardium	Acute pericarditis Chronic effusion Constrictive pericarditis
Vascular tree	Premature coronary artery disease Myocardial infarction Asymptomatic coronary artery disease Aortic arch calcification Carotid stenosis Transient ischemic attack/stroke Peripheral vascular disease
Endocardium	Valvular disease
Myocardium	Myocarditis Cardiomyopathy Chronic heart failure Diastolic dysfunction
Conduction system	Heart block

is the use of computed tomography for dose planning and the transition to 3D dose planning systems. These developments provide an opportunity for the definition of target and organs at risk volumes as the heart and help to evaluate the cumulative doses.[11] However, the cardiotoxic potential of some chemotherapy agents such as anthracyclines should also be kept in mind. Even after a follow-up time of 25 years, 3-5 times higher cardiovascular disease risk is reported in a population-based study of 5-year survivors of HL, and authors report the 30-year cumulative incidence of any cardiovascular disease risk as 34.5%.[12] Dose and response association has been shown in several studies, and the incidence of cardiovascular disease decreases with smaller mediastinal RT dose and volume of the heart.[13,14] It has been shown that a cardiac dose of above 15 Gy increases the risk of congestive heart failure, myocardial infarction, pericardial disease, and heart valve abnormalities by 2-6-fold compared to survivors without RT.[14]

Pericarditis

Acute pericarditis is a rare situation and can develop during or within weeks after RT due to inflammation.[15] It can emerge as asymptomatic or symptomatic and spontaneous regression of effusion may occur, but in some patients, pericardiocentesis is indicated because of large pericardial effusion.[16] Chronic pericarditis appears months to years after RT. Even with

large pericardial effusions, most patients are usually asymptomatic. It may be detected as coincidentally, and treatment of acute pericarditis contains conventional therapy such as nonsteroidal anti-inflammatory drugs and colchicine.[17] The most severe form of radiation-induced pericardial disease is constrictive pericarditis and associated with a poor outcome.[18] Symptoms are the same as intractable congestive heart failure, and definitive treatment is pericardiectomy surgery.[19]

CAD

CAD occurs as a result of damage to the vascular endothelium.[20] Dose-response relationship and 2.2-7.7-fold increased risk of fatal myocardial infarctions have been documented in a study of HL survivors who had prior treatments with supradiaphragmatic RT with 19 years median time interval from diagnosis.[8] The age, proximity to the heart, radiation dose, and presence of coexisting risk factors are effective in the development of CAD.[7] Although the risk of restenosis in these patients is higher than usual, the treatment of radiation-induced CAD is similar to the general population.[2] The rate of abnormal ventricular images at rest is reported as 21.4% in a study of 294 asymptomatic HL patients who do not have CAD, and this suggests prior myocardial injury. At the same time, perfusion defects are detected in 14% of patients during stress testing, and coronary angiography was performed in 90% of patients with perfusion defects. Stenosis more than 50% is in 55% of the patients. At the end of a median of 6.5 years of follow-up, screening led to bypass graft surgery performed in 2.4%, and coronary events developed in 7.8% of 294 patients.[21] In a study of HL survivors age 17-28 years, coronary abnormalities are detected as 6.8 times more in patients who received RT compared with patients who are not.[22] It has been shown that stenotic segments received higher doses compared with non-stenotic segments in HL patients treated RT.[23]

Non-invasive testing such as computed tomography angiography, single-photon emission computed tomography, or stress echocardiography should be considered in high-risk patients.[1,2,24]

HVD

HVD is frequently seen in patients with RT-induced heart disease, and the aortic and mitral valves are more commonly involved. A higher incidence of aortic regurgitation (60% vs. 4%), aortic stenosis (16%

Table 2 Dose recommendations and constraints[37-39]

Dose recommendations	
Radiation alone	<ul style="list-style-type: none"> • As primary treatment for lymphocyte predominant Hodgkin lymphoma <ul style="list-style-type: none"> - Clinically involved and adjacent uninvolved nodes: 30-36 Gy • As primary treatment for classic Hodgkin lymphoma <ul style="list-style-type: none"> - Clinically involved sites: 30-36 Gy - Clinically uninvolved sites: 30 Gy
Radiation following chemotherapy in a combined modality program	<ul style="list-style-type: none"> • Patients in CR after chemotherapy: 20-30 Gy <ul style="list-style-type: none"> - For pediatric or adolescent patients: 15-24 Gy - In some programs of short chemotherapy for bulky or advanced-stage disease (e.g., Stanford V), the recommended radiotherapy dose is 30-36 Gy • Patients in PR after chemotherapy: 30-40 Gy
Constraints for heart	Heart mean dose <26 Gy, heart D100 <30 Gy, heart V30 <20%, heart V25 <10% Left atrium V25 <63%, left ventricle V30 <25%, right ventricle V30 ≤65% Pericardium V30 ≤46%, mean ≤26 Gy

vs. 0%), and mitral regurgitation (52% vs. 26%, respectively) has been reported in asymptomatic HL survivors after 20 years.[25]

Authors reported 89 (aortic valve in 71% and the mitral valve in 47%) patients with moderate valve disease and increased risk with radiation dose in a case-control study from a cohort of 1852 HL 5-year survivors (diagnosed at ages 15-41 years). The risk of HVD is reduced with lower doses and newer techniques in recent decades. It has been stated that in patients treated with 20-30 Gy, the 30-year risk of HVD will be increased by only about 1.4% compared with the general population.[26]

Patients with valve disease should be evaluated with echocardiography at regular intervals, and the patients should be educated on signs of progression. Surgery should be considered in patients with severe valve disease. Other treatment strategies such as transcatheter aortic valve replacement and percutaneous mitral valve clips may be considered in appropriate patients.

Myocarditis, Cardiomyopathy

Damage to microvasculature after RT is one of the causes of myocardial injury.[27] Diffuse myocardial fibrosis can occur, often after the dose of >25-30 Gy. Restrictive cardiomyopathy represents advanced myocardial damage with severe diastolic dysfunction and signs and symptoms of heart failure.[27] The risk of developing symptoms of congestive heart failure after RT is 5.9%.[14]

A study includes young survivors exposed to anthracycline, RT, or both are evaluated. Abnormal global longitudinal strain (GLS) results are associated with RT at 1-19.9 Gy (relative risk [RR]: 1.38), 20-29.9 Gy (RR:

1.65), and >30 cGy (RR: 2.39), and anthracycline dose above 300 mg/m² was associated with abnormal GLS (RR: 1.72).[28]

Echocardiography is recommended as the first choice of the left ventricular ejection fraction (LVEF) evaluation with the use of GLS. Angiotensin-converting enzyme inhibitors and β -blockers should be initiated if the LVEF is decreased by 10%.[24,29]

Conduction System

The conduction system is rarely involved after RT, and ECG findings may range from non-specific ST-T changes to low voltage and right bundle branch block. [30,31] The right bundle branch block is commonly associated with mediastinal RT. The complete atrioventricular block is a serious situation and extensive heart disease with CAD, valve disease, and constriction is concomitantly present in a large fraction of patients who developed complete heart block.[32]

RT Application and Dose Constraints for Heart

In the current successful treatment of HL, RT is the cornerstone component. Although RT has been used alone to cure in most of the patients in decades, it is still the most effective single agent and it alone remains for treatment choice in patients with early-stage lymphocyte predominance HL (LPHL) and for selected patients with classical HL (cHL) who have contraindications to chemotherapy. Combined modality regimens are preferred in most HL patients currently. Classic RT fields, doses, and techniques have fundamentally

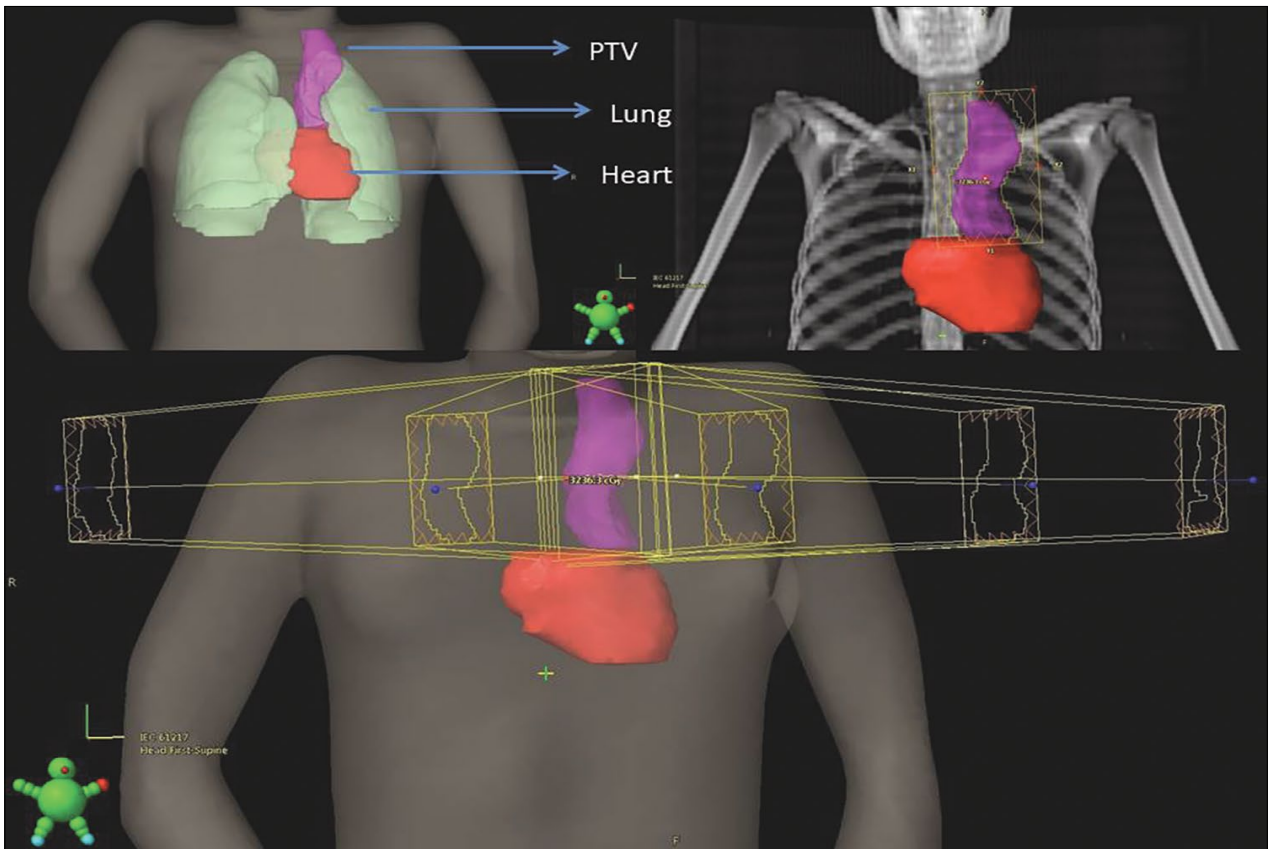


Fig. 1. Contour and radiotherapy field images of a classic Hodgkin lymphoma patient treated with involved-nodal radiotherapy.

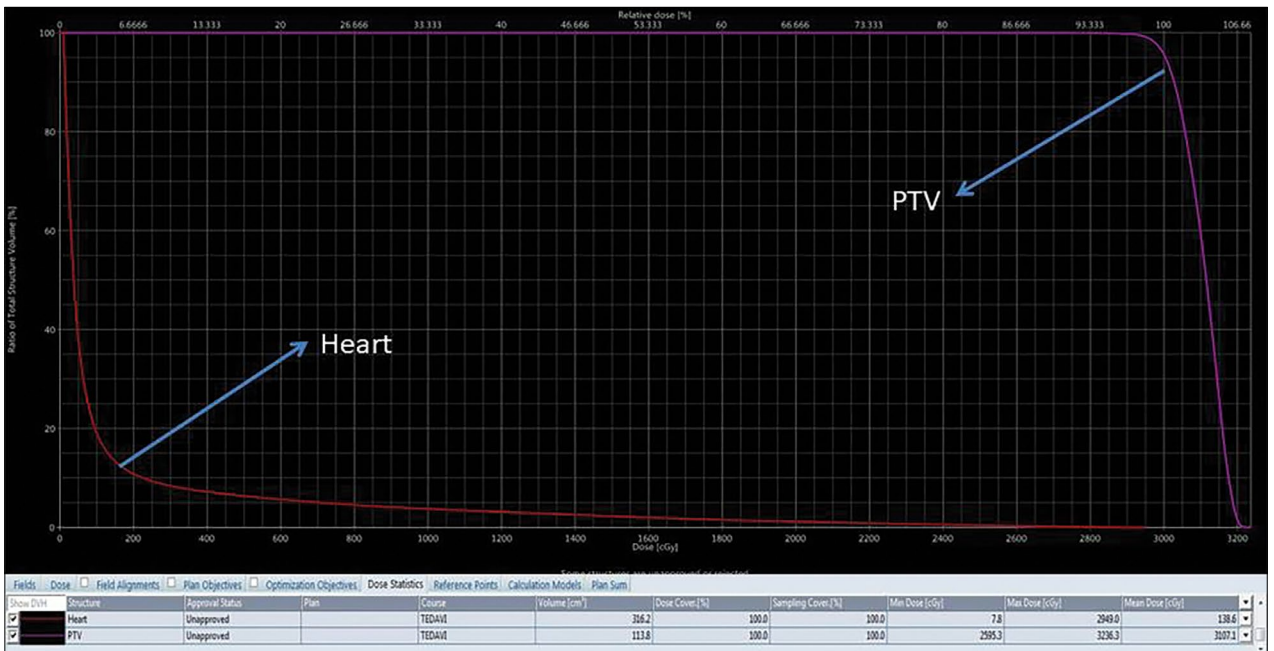


Fig. 2. Dose-volume histogram image of a classic Hodgkin lymphoma patient treated with involved-nodal radiotherapy.

changed over the years.[33,34] The large RT fields known as the mantle, inverted Y, and total lymphoid irradiation are left in place to involved-field RT and then to the involved-nodal RT (INRT)/involved-site RT in years.[35-37] Dose recommendations for LPHL/CHL and dose constraints for the heart are presented in Table 2.[37-39] Contour, RT fields, dose-volume histogram, and dose color wash images of a cHL patient treated with 30 Gy INRT in accordance with these references are presented in Figures 1-3.

Conclusion

Although modern RT techniques in today, cancer patients such as lymphoma initially treated with RT are at increased risk of developing cardiovascular disease because of prior RT doses, cardiovascular risk factor positivity, and chemotherapy agents such as anthracycline. Lifelong follow-up and surveillance because of the development of radiation-induced cardiotoxicity are necessary, and all survivors with risk factors should be treated.

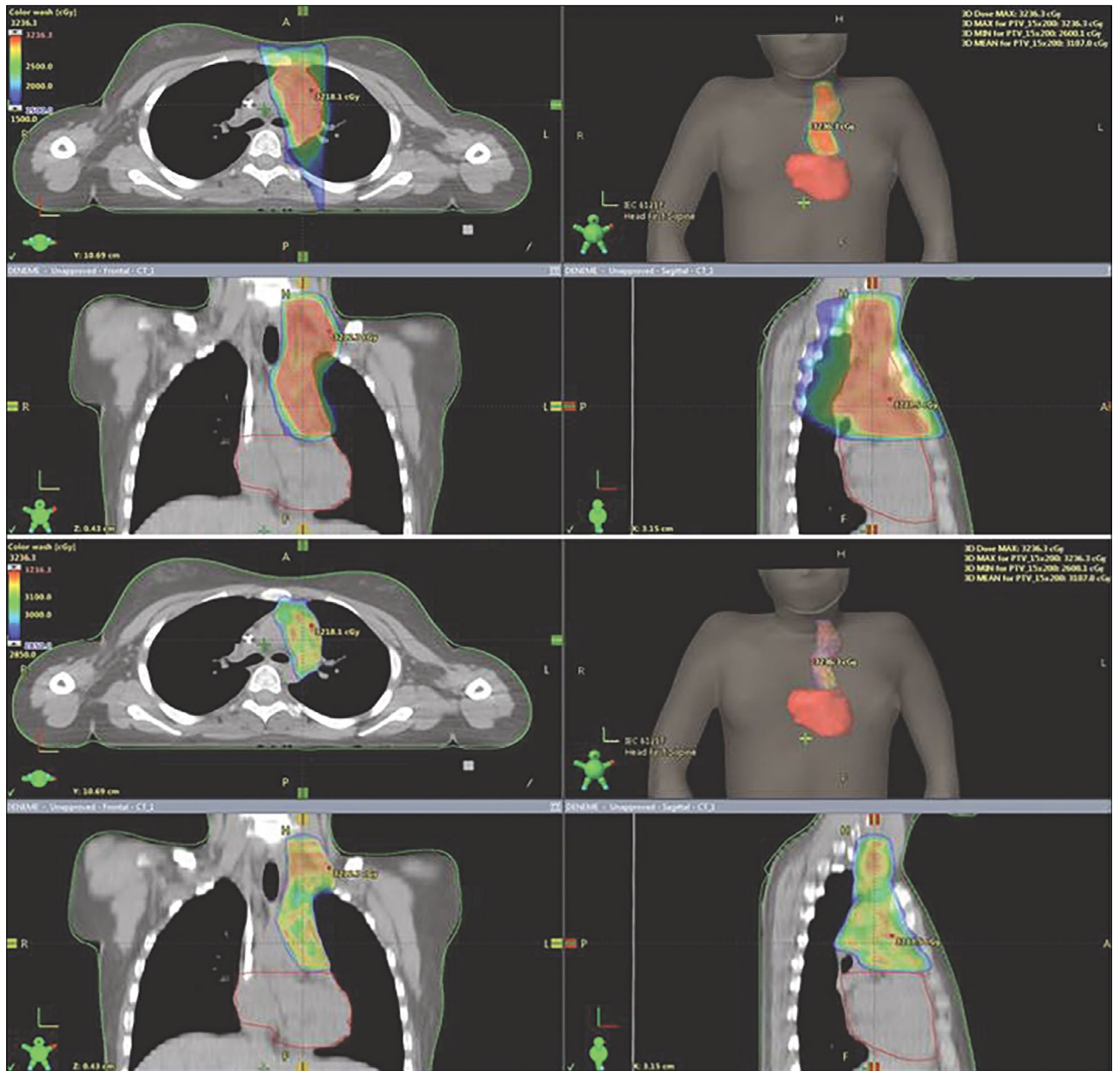


Fig. 3. About 50% and 95% dose color wash images of a classic Hodgkin lymphoma patient treated with involved-nodal radiotherapy.

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