

Review Article

Assessment of cardiac sparing in radiotherapeutic management of mediastinal Hodgkin lymphoma (hl) during childhood and adolescence

Omer Sager*, Murat Beyzadeoglu, Selcuk Demiral, Ferrat Dincoglan, Hakan Gamsiz, Bora Uysal, Onurhan Colak, Fatih Ozcan and Bahar Dirican

Department of Radiation Oncology; University of Health Sciences, Gulhane Medical Faculty, Ankara, Turkey

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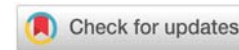
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***Corresponding author:** Dr. Omer Sager, Department of Radiation Oncology; University of Health Sciences, Gulhane Medical Faculty, Gn.Tevfik Saglam Cad. 06018, Etlik, Kecioren, Ankara, Turkey, Tel: +90 312 304 4683; Fax: +90 312 304 4680; E-mail: omersager@gmail.com

ORCID: <https://orcid.org/0000-0001-7866-2598>

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Abstract

Lymphomas constitute the most frequent hematologic malignancies. HL is a rare type of B cell lymphoma featured with Reed Sternberg cells. Treatment of HL may be considered among the greatest success stories in oncology. Improvements in treatment of HL have rendered quality of life an important aspect of management given the long life expectancy of younger patients, particularly the children and adolescents.

The heart may be partly exposed to irradiation in radiotherapeutic management of mediastinal HL. Late effects of irradiation may include stenosis, regurgitation, and fibrosis of the cardiac conduction pathways which may result in late onset arrhythmias and conduction defects, angina pectoris, valvular disorders, coronary artery disease and myocardial infarction. Patients receiving RT to the mediastinum may suffer from adverse cardiovascular effects of irradiation due to coronary atherosclerosis formation which may occur despite the lack of any cardiovascular risk factors, and an asymptomatic period of several years may precede presentation with coronary heart disease given the slow process of intimal hyperplasia and collagen deposition. It may take several years after RT to diagnosis of these complications.

Normal tissue sparing Radiation Therapy (RT) techniques allow for improved targeting and normal tissue sparing in HL management. A relatively newer breakthrough has been the introduction of proton therapy with its unique characteristics. Herein, we provide a concise review of evolving RT techniques for management of mediastinal HL with focus on cardiac sparing.

Introduction

Lymphomas constitute the most frequent hematologic malignancies, and typically fare better than most solid cancers [1-3]. Hodgkin Lymphoma (HL) and Non Hodgkin Lymphoma (NHL) have distinct characteristics. HL is a rare type of B cell lymphoma featured with Reed Sternberg cells or lacunar histiocytes as giant malignant lymphoid cells which are

typically positive for CD15 and CD30 but negative for CD20 and CD45. Reed Sternberg cells are considered to be diagnostic, however, the diagnosis should be based on the presence of the consistent cellular background and immunophenotyping results [4]. As an important cancer during the childhood and adolescence, HL may involve peripheral lymph nodes and rarely the liver, lungs, bone marrow, gastrointestinal or genitourinary tract. A bimodal age distribution is typical with one peak at



the age of about 20 years and the other at the age of about 70 years. HL may be subdivided into lymphocyte predominant HL and classic HL (CHL) with respect to genotypic, phenotypic, morphological, and clinical findings [4]. CHL subtypes include the nodular sclerosing CHL which is the most frequent type in children, lymphocyte depleted CHL, mixed cellularity CHL, and lymphocyte rich CHL [4].

Treatment of HL may be considered among the greatest success stories in oncology [5]. While the disease was considered as a lethal malignancy decades ago, contemporary management with irradiation and systemic treatment has provided excellent prognosis with long term survival outcomes in the millennium era [5-8]. Improvements in treatment of HL have rendered quality of life an important aspect of management given the long life expectancy of younger patients, particularly the children and adolescents. Normal tissue sparing Radiation Therapy (RT) techniques minimizing cardiac exposure have been introduced and adopted in clinical practice to achieve an improved therapeutic ratio for HL. Herein, we provide a concise review of evolving RT techniques for management of mediastinal HL with focus on cardiac sparing.

Cardiac sparing RT techniques for mediastinal HL management

RT is a principal modality of management for HL, utilized as the single treatment to achieve cure in selected patients [9]. Nevertheless, long life expectancy of children and adolescents with HL underscore the importance of quality of life of treated patients. While RT is an effective treatment modality, it is not devoid of adverse effects. Several authors have addressed the side effects of irradiation with focus on cardiotoxicity [10-25]. Systematic reviews and metaanalyses of long term risk of cardiovascular disease and mortality in lymphoma survivors revealed that risk of cardiovascular events is increased in lymphoma survivors compared with the general population, which emphasizes the importance of cardiovascular screening for these patients [26-28].

The heart may be partly exposed to irradiation in radiotherapeutic management of mediastinal HL. Late effects of irradiation may include stenosis, regurgitation, and fibrosis of the cardiac conduction pathways which may result in late onset arrhythmias and conduction defects, angina pectoris, valvular disorders, coronary artery disease and myocardial infarction [29-31]. Patients receiving RT to the mediastinum may suffer from adverse cardiovascular effects of irradiation due to coronary atherosclerosis formation which may occur despite the lack of any cardiovascular risk factors, and an asymptomatic period of several years may precede presentation with coronary heart disease given the slow process of intimal hyperplasia and collagen deposition [29-31]. It may take several years after RT to diagnosis of these complications [32-34].

Over the years, there have been considerable advances in the discipline of radiation oncology including adoption of contemporary RT strategies such as Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), Adaptive Radiation Therapy (ART), Breathing Adapted

Radiation Therapy (BART), and radiosurgical applications to improve outcomes of management [35-41]. In the context of HL therapy, these strategies along with combination of precise RT approaches allowed for improved targeting and normal tissue sparing [42-52]. The recent expert consensus on the use of IMRT and IGRT for Hodgkin's lymphoma involving the mediastinum states that mean whole heart dose of < 5 Gy and mean left ventricle dose of < 2 Gy may be recommended as dose objectives for the heart, and contemporary techniques may aid in respecting critical organ dose constraints [42]. Nevertheless, a relatively newer breakthrough has been the introduction of proton therapy with its unique characteristics [53-63]. Studies with proton therapy consistently reported superior normal tissue sparing, particularly when combined with contemporary techniques. The study by Lautenschlaeger et al. focusing on pediatric patients and adolescents with HL reported significant reduction in doses to critical organs and integral body dose with proton therapy [63]. The authors concluded that these reductions could translate into decreased risk of late toxicities and secondary malignancies which is particularly important for children and adolescents [63].

While logistical issues, access to therapy, treatment costs and availability are still important considerations for proton therapy, pediatric patients and adolescents with mediastinal HL may benefit from the favorable characteristics of this treatment modality given their excellent prognosis and life expectancy.

Conclusion and future perspectives

Despite the significant advances in management of children and adolescents with mediastinal HL using RT, there still remains room for improvement for further achievements. Further studies are required to shed light on management of mediastinal HL with an improved toxicity profile and optimal cardiac sparing.

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