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Review

Cardiotoxicity of mediastinal radiotherapy☆

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ARTICLE INFO

Article history:
Received 15 March 2019
Accepted 21 September 2019
Available online 30 October 2019

Keywords:
Cardiotoxicity
Mediastinal radiotherapy
Mediastinal tumours
Dose-volume predictors
Normal tissue complication probability

ABSTRACT

Aim: To explore available recent literature related to cardiotoxicity following mediastinal radiation.

Background: Radiotherapy-related heart injury is well documented, with no apparent safety threshold dose. The number of long-term cancer survivors exposed to mediastinal radiotherapy at some point of their treatment is increasing. Heart dosimetric parameters are of great importance in developing a treatment plan, but few data are available regarding radiosensitivity and dose-volume constraints for specific heart structures.

Materials and Methods: In October 2018, we identified articles published after 1990 through a PubMed/MEDLINE database search. The authors examined rough search results and manuscripts not relevant for the topic were excluded. We extracted clinical outcomes following mediastinal radiotherapy of childhood cancers, lymphoma, medulloblastoma, thymic cancers and hematopoietic cell transplantation survivors and evaluated treatment planning data, whenever available.

Results: A total of 1311 manuscripts were identified in our first-round search. Of these manuscripts, only 115 articles, matching our selection criteria, were included.

Conclusions: Studies uniformly show a linear radiation dose-response relationship between mean absorbed dose to the heart (heart-D_{mean}) and the risk of dying as a result of cardiac disease, particularly when heart-D_{mean} exceeds 5 Gy. Limited data are available regarding dose-volume predictors for heart substructures and the risk of subsequent cardiac toxicity. An individual patient's cardiotoxicity risk can be modified with advanced treatment planning techniques, including deep inspiration breath hold. Proton therapy is currently showing advantages in improving treatment planning parameters when compared to advanced photon techniques in lymphoma, thymic malignancies, malignant mesothelioma and craniospinal irradiation.

Abbreviations: RR, relative risks; D_{mean}, mean absorbed radiation dose in a specified volume; D_{max}, maximum absorbed dose in a specified volume; NTCP, normal tissue complication probability; HR, hazard ratio; OR, odds ratio; OAR, organs at risk; V_x, receiving at last x Gy; IMRT, intensity modulated radiation therapy; 2D-RT, two-dimensional radiotherapy; 3D-CRT, three-dimensional conformal radiation therapy; G, grade; Gy, Gray; EQD_2, equivalent dose in 2 Gy fractions; VMAT, volumetric modulated arc therapy; HT, Helical tomotherapy; CSI, craniospinal irradiation; CI, confidence interval; CVD, Cardiovascular disease; TBI, total body irradiation; PTV, planning target volume; Mv, megavoltage; OAR, organs at risk; ISRT, involved site radiotherapy; INRT, involved node radiotherapy; IFRT, involved field radiotherapy; LAD, left anterior descending artery.

☆ Article from the Special Issue on Cardiotoxicity of Radiotherapy

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https://doi.org/10.1016/j.rpor.2019.09.002
1507-1367/

1. Background

The number of long-term cancer survivors is increasing, primarily due to the successful implementation of new diagnostic and treatment strategies in recent decades. Radiotherapy, as one of the fundamental modalities of cancer care, is improving progression-free and overall survival in many thoracic malignancies.[1,2] Nonetheless, exposure to radiation therapy increases long-term survivors' relative risks (RR, 1.2–3.5) for clinically important cardiac events, such as congestive heart failure, pericarditis or ischemic heart disease. Subclinical abnormalities can be detected with accurate diagnostic methods in ≥50% of patients,[3] depending on the screening method and heart-absorbed dose. Toxic effects of mediastinal radiotherapy on heart substructures, such as pericardium, myocardium, conducting system, coronary arteries and heart valves are well documented.[4–11] Most clinical data on the association between heart dosimetric parameters and cardiotoxicity come from adult Hodgkin lymphoma, breast cancer, lung cancer, esophageal cancer and childhood cancer survivors.[7] The risk of cardiac toxicity and time interval between mediastinal radiotherapy and clinical manifestation of cardiovascular disease (CVD) may be both related to heart-absorbed dose and irradiated heart volume, which are further associated with planning target size and its location in the mediastinum, vicinity to specific cardiac substructures, prescribed radiotherapy dose, technique and individual anatomy.[3,7,12] Baseline patient and treatment-related cardiovascular risk factors, including smoking, physical activity, diet, obesity, arterial hypertension, dyslipidaemia, diabetes mellitus, family history of cardiovascular diseases, age, gender and chemotherapy regimens may additionally affect overall risk of radiation-induced cardiac injury.[3,5]

When the whole heart absorbs small radiation doses, cardiac injury may become clinically manifested within the first few years after radiotherapy and continue to be of great significance decades after radiation exposure.[5,13–15] That kind of association was observed with a linear dose-effect correlation between heart-D_{mean} and late CVD in breast cancer,[5,16,17] paediatric[4,18] or lymphoma[11,19,20] survivors, with no apparent heart-D_{mean} threshold. On the contrary, when prescribed doses to the clinical target in the mediastinum are typically higher (≥40–50 Gy), smaller parts of the heart may absorb higher radiation doses. Evidence from oesophageal[21] and lung cancer[8,12] studies reveals that excessive dose to the heart may put patients at a higher risk of non-cancer related death in the first few years after completion of radiation therapy. Heart-V_{20} (hazard ratio, HR 1.008, $p < 0.001$) and heart-V_{40} (HR 1.013, $p < 0.001$) were associated with decreased survival in univariate analysis of the RTOG 0617 randomized trial in locally advanced lung cancer. Importantly, heart-V_{40} (HR 1.012, $p < 0.001$) remained significantly associated with overall survival also in multivariate analysis.[12]

The aim of this review is to résumé available clinical and treatment planning data regarding cardiotoxicity of mediastinal (non-lung and non-oesophageal) radiotherapy, including thoracic tumours such as lymphoma or thymic malignancies. We also reviewed data regarding craniospinal (CSI) and total body irradiation (TBI).

2. Materials and methods

Published manuscripts were identified through a PubMed/MEDLINE search of the National Library of Medicine using combinations of the following keywords: cardiotoxicity, cardiac toxicity, cardiovascular diseases, cardiovascular complications, cardiac dysfunction, cardiovascular effects, cardiac complications, cardiac injury, normal tissue complication probability (NTCP), radiotherapy, radiation dosage, dose-estimation models, dose-volume predictors, radiotherapy dosage, radiation therapy, radiation-induced, irradiation, dosimetric study, lymphoma, thymoma, mesothelioma, craniospinal irradiation, total body irradiation, medulloblastoma, cancer of the mediastinum, mediastinal cancer, mediastinum cancer, mediastinum neoplasms, mediastinal neoplasms, mediastinal tumours, mediastinal radiation. In the first evaluation round, we examined rough search results and excluded articles not relevant for the topic. Through hand searching of the relevant articles' reference lists, we found additional references. We considered only English language literature and limited our search to articles published after 1990.

3. Results

An initial search of the literature retrieved 1311 results. The final selection resulted in 212 manuscripts, and 97 of them were excluded because of several reasons, as follows: the content of the article was not focused on cardiac toxicity of mediastinal irradiation, duplicated items or the manuscripts presented case reports. Whenever possible, we further classified studies into clinical or treatment planning/dosimetric comparison groups.

4. Cardiotoxicity in survivors of childhood and adolescent cancer

A linear dose-response relationship between the average dose to the heart and the risk of cardiac mortality (estimated excess RR at 1 Gy, 60%) was brought forward in a study on childhood cancer survivors by Tukenova et al. in 2010.[4] In their study cohort of 4122 patients, including Hodgkin and non-Hodgkin lymphoma survivors diagnosed before 1986, anthracycline chemotherapy (cumulative dose >360 mg/m^2) and heart-D_{mean}, particularly when it exceeded 5 Gy (RR ≥ 12.5), were both associated with an increased risk of dying of cardiac disease.[4] In a retrospective cohort study by Mulrooney et al., survivors of various paediatric cancers were significantly more likely to suffer from a pericardial disease, congestive heart failure, myocardial infarction or valvular disease than siblings, with a reported HR of 6.3, 5.9, 5.0 and 4.8, respectively.[22] Heart-D_{mean} ≥15 Gy significantly increased the likelihood of symptomatic cardiac injury.[22]

In another study, symptomatic cardiac events were observed in 50 out of 1362 childhood cancer survivors, who were diagnosed between 1966 and 1996 and were at least five years cancer-free, with a median follow-up of 22.5 years since cancer diagnosis (range, 4.0–44.5). Two-hundred and sixty-six

patients were exposed to the radiation, due to TBI, CSI, whole abdominal irradiation or irradiation of the thoracic structures with a median cardiac absorbed dose (equivalent dose in 2 Gy fractions, EQD_2) ranging from 15.75 to 30.14 Gy.[23] In the multivariate analysis, a higher anthracycline dose (HR 1.7 per 100 mg/m^2), a higher cardiac irradiation dose (HR 1.8 per 10 Gy EQD_2) and the presence of congenital heart disease (HR 12.0) all significantly increased the risk of a symptomatic cardiac event.[23]

Chow et al. proposed an individual prediction model of ischemic heart disease succeeding childhood cancer treatment based on an observational study on a large population of 5-year childhood cancer survivors (N = 13.050) and a control group of 4023 siblings. Low-, moderate- and high-risk categories were identified in a prediction model, which included sex, chemotherapy and estimated heart-specific absorbed radiation dose. The model proposed an increased risk of cardiotoxicity for chest radiation, particularly when the absorbed dose in the thorax exceeded 5 Gy. Cumulative incidences for ischemic heart disease at age 50 years were 7.7% (95% confidence interval, CI, 6.3–9.1%) and 1.2% (95% CI, 0.4–2.0%) for survivors of childhood cancer and control group, respectively. Among low-, high-risk and control groups, cumulative incidences were as follows: <5%, 20% and 1% ($p < 0.001$), respectively.[24] Nevertheless, it is worth bearing in mind that all long-term data for paediatric cancer survivors are derived from two-dimensional radiotherapy (2D-RT) treatment planning and reconstructed three-dimensional estimates of the absorbed heart doses.

5. Cardiotoxicity after mediastinal radiotherapy for Hodgkin and non-Hodgkin lymphoma survivors

Treatment of lymphoma patients has changed dramatically during recent decades, with the de-escalation of both chemotherapy and radiotherapy in order to diminish early and late toxicity while at the same time not compromising control of the disease. Most of our knowledge regarding cardiotoxicity in long-term survivors comes from radiation therapy delivered 20–30 years ago using mantle field and prescribed radiation doses of ≥40 Gy. Today, radiation fields are significantly smaller, prescribed doses are lower and, in some cases, radiotherapy is no longer indicated. Currently, doses of 20–36 Gy are typically prescribed to a more precisely defined target volume depending on the stage of the disease, type of lymphoma and response to chemotherapy.[1]

Before linear accelerators and three-dimensional conformal radiotherapy (3D-CRT) treatment planning became widely available, the 2D-RT approach with an anterior mediastinal field with or without boost dose to the posterior mediastinum was typically used. Besides, a Cobalt-60 unit lower mean energy of 1.25 MV resulted in high-dose areas near the body surface, anatomically corresponding to anterior portions of the heart. 3D-reconstructed doses to the heart and right coronary artery in a study by Vordermark et al. range up to 48–58 Gy, with a median maximal dose (D_{max}) corresponding to 128% of the prescribed dose.[25] The modern anterior-posterior opposing-beam mantle technique with photon energies of 4–6 MV generates much lower maximum doses in the anterior cardiac region, resulting in lower cardiotoxicity risk.[25,26]

5.1. *Cardiac mortality and morbidity after radiation treatment for lymphoma survivors*

Cardiovascular death is the third most common cause of death of lymphoma survivors after disease recurrence and secondary cancer.[13,27] Compared to the general population, Hodgkin and non-Hodgkin lymphoma survivors are estimated to have 5.3–7.3 times increased risk of long-term cardiovascular mortality.[28] In a large meta-analysis by Boyne et al., including more than 61,000 survivors, treated between the years 1940 and 2006, the association was even more significant for Hodgkin lymphoma survivors treated before the age of 21.[28] Retrospective studies with median follow-up of 7–15.6 years are consistently reporting an RR of 3.1–6.7 for myocardial infarction or sudden cardiac death.[29,30]

The most frequently occurring CVDs in Hodgkin lymphoma survivors are valvular heart disease (21–41%) and coronary heart disease (17–23%), followed by heart failure (8–17%), conduction disorders (12%) and pericardial abnormalities (10%).[30–33] The 40-year cumulative incidence of CVD with multimodality treatment (mediastinal radiotherapy and anthracycline-containing chemotherapy) could be as high as 50%, with more than half of these patients developing multiple events.[31] The risk for various cardiovascular diseases remains increased at least 25–40 years after treatment and is especially high in younger patients (<20–25 years of age).[31,34]

5.2. *Coronary artery disease*

Chest irradiation, with or without chemotherapy, predisposes patients to a higher presence, greater severity, more considerable extent and more proximally located coronary artery disease (CAD) compared with matched non-irradiated controls.[35] Coronary CT abnormalities can be detected early, within the first five years after treatment and the risk remains high ≥15 years after radiotherapy.[36] Arterial stiffness, which seems to occur soon after radiation, is frequently used as an early marker of CVD.[37] Van Leeuwen-Segarceanu et al. found increased arterial stiffening in Hodgkin lymphoma survivors treated with mediastinal radiation and this increase was most evident in patients treated at an older age (>35–40 years).[38] RR for death attributed to acute myocardial infarction for those who received more than 35 Gy to the mediastinum is estimated to be 7.5.[39]

5.3. *Valvular heart disease*

Left-sided valves (aortic and mitral ones) are more often involved than right valves and regurgitation is more common than stenosis.[40–44]. Dysfunction is mostly mild, but the risk of moderate or severe dysfunction is much higher than in the general population.[30,33,42] For clinically relevant valvular disease, a latency greater than ten years and a high risk of progressive valvular deterioration during the second and third decade after treatment have been described.[44] Prevalence

increases with time following irradiation and seems to be independent of age.[41,42]

5.4. *Pericardial disease*

On average, a mean absorbed dose of 40 Gy to the mediastinum increases the prevalence of the asymptomatic pericardial disease tenfold, but the clinically evident pericardial disease is rare.[30,45] In a study by Wei et al., clinical indicators of pericardial disease better correspond with dose-volume parameters derived from the dose-volume histograms of the pericardium than with those of the whole heart. The risk for pericardial effusion is particularly high for pericardium-D_{mean} > 26 Gy and pericardium-V_{30} > 46%.[3,46] In a retrospective study on 325 Hodgkin lymphoma survivors, the pericardial thickening was reported in 21% of patients after a median follow-up of 11.2 years, in comparison with 2.5% in the general population. No patient had wall-motion abnormalities or Doppler findings suggestive of constrictive pericarditis.[30] Lund et al. documented pericardial thickening in 15% of the total 116 patients, who received a median radiation dose of 40.6 Gy to the mediastinum. In most cases, there were no signs of hemodynamic impairment.[47] Pericardial disease requiring pericardiectomy or pericardiocentesis occurred in 0.7% of 1279 Hodgkin lymphoma survivors after a median mediastinal absorbed dose of 40 Gy. The absolute excess risk for a pericardial procedure was 4.69 per 10,000 person-years of follow-up or 0.05% per year.[45]

5.5. *Myocardium and heart failure*

Myocardium exposure to high radiotherapy doses leads to myocardial fibrosis and, consequently, to restrictive cardiomyopathy. The primary mechanism of heart failure in restrictive cardiomyopathy is diastolic dysfunction. Congestive heart failure can also be associated with other radiation-induced heart conditions such as constrictive pericarditis, CAD, ischaemic and valvular heart diseases and most commonly occurs late in a series of events.[36,48] Heart failure risk increases with time and is three- to sevenfold more common compared to non-irradiated patients, mainly when absorbed heart-D_{mean} is higher or equal to 30 Gy.[34,41] Forty-year cumulative incidence of heart failure and cardiomyopathy is rather high, reaching 14–25%.[31,33,34]

5.6. *Asymptomatic cardiotoxicity*

Cardiac abnormalities are frequently found in asymptomatic lymphoma survivors screened with echocardiography, myocardial perfusion scintigraphy, electrocardiogram (ECG) or cardiac MRI. The prevalence increases with time post-radiation treatment and ranges from 4% to almost every screened patient, depending on screening method, prescribed dose, heart absorbed dose and dose to its substructures.[32,33]

5.7. *Dose-volume predictors of cardiotoxicity*

Only a few studies have examined dose-response relationships for radiation-induced cardiotoxicity in lymphoma survivors (Table 1). In mediastinal radiotherapy for Hodgkin lymphoma patients, the heart generally absorbs a more homogenous dose — heart-D_{mean} is significantly higher and patients are typically younger at the time of treatment compared to breast cancer patients. A large case-control study of 2617 Hodgkin lymphoma survivors evaluated dose-response relationship between heart-D_{mean} and risk of CAD after mediastinal radiotherapy.[20] The authors confirmed a linear radiation dose-response relationship described in previous studies and indicated that there is no threshold dose (Fig. 1). Neither chemotherapy in general nor a specific chemotherapeutic agent was associated with CAD risk. It was also demonstrated that higher physical activity levels may decrease the risk for CAD development, while hypertension, obesity and recent smoking are independent risk factors for higher risk of CAD.[20] Cella et al. linked the risk of asymptomatic alteration of valvular function with dose-heart volume constraints for the whole heart and specific cardiac substructures. In their study on 56 patients, 32.1% of patients developed valvular regurgitation and/or stenosis after a median follow-up of 70.5 months. Left atrium (LA), left ventricle (LV) and right ventricle (RA) dosimetric parameters were all associated with a higher risk of mitral, aortic or tricuspid valve dysfunction.[49] Moreover, in another publication, the authors emphasized the importance of jointly considering lung dose-volume constraints and lung volume in predicting subclinical radiation-related injury, resulting in valvular dysfunction.[19] Cutter et al. assessed the relationship between radiation dose to the heart valves and the subsequent risk of clinically significant valvular dysfunction. A non-linear relationship was found between valve-D_{mean} and valvular dysfunction with a progressive increase in valvular dysfunction rates with valve-D_{mean} > 30 Gy. The authors estimate that 30-year risk of significant valvular dysfunction will be increased by only approximately 1.4% for Hodgkin lymphoma patients treated with modern mediastinal radiotherapy using 20–30 Gy.[11]

5.8. *Target volumes and radiotherapy techniques*

Reduction in target volume and total prescribed dose, using modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) or proton therapy and deep inspiration breath hold (DIBH) are all ways to reduce radiation dose to the heart and its substructures.

Compared to mantle field radiotherapy, involved field radiotherapy (IFRT) or involved node radiotherapy (INRT) reduce heart-D_{mean} by 35–72% [50,51] The average reduction of heart-D_{mean} by an absolute of 19.8 Gy in a study by Maraldo et al. would, interpreting data from van Nimwegen.study, lead to an expected 146% relative reduction in the risk of ischaemic heart disease.[20,51] A significant difference in heart-D_{mean} was shown in a treatment planning study, taking into account four different volumes and two different prescribed doses. Heart-D_{mean} ranged from 6.7 to 21.2 Gy, depending on target volume size and prescribed dose.[52] Similar reductions of heart-D_{mean} (range, 8.4–21.9 Gy) and also heart-V_{30} (range, 2.1–29.1%) were calculated in a dosimetric comparison study by Murray et al..[43] Studies coherently report the benefit of IMRT versus 3D-CRT in lowering the mean doses to the heart and cardiac subunits. While typical heart-D_{mean} reduction with IMRT is in the

Table 1 – Studies investigating dose-volume predictors for radiation-induced cardiotoxicity in lymphoma survivors. Abbreviations: D_{mean}, mean dose absorbed to the specified volume; D_{max}, maximum absorbed dose to the specified volume; ↑, higher; AMI, acute myocardial infarction; ERR, the excess relative risk; CAD, coronary artery disease; HL, Hodgkin lymphoma; 2D-RT, two-dimensional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; RT, radiotherapy; V_x, receiving at last x Gy; LA, left atrium; LV, left ventricle; RV, right ventricle; VD, valvular dysfunction; CAO, coronary artery origin; CCTA, coronary CT angiography; OR odds ratio; NA, not available; HR, hazard ratio; LAD, left anterior descending artery, LCX, left circumflex coronary artery; * indicates average; ♦ indicates median; • 8.9% and 20.8% of patients did not receive radiotherapy in cases and controls group, respectively; § median age was not reported; φ, 83.3% of patients received radiation.

Author and year of publication	Type of study	Number of patients	Time at HL diagnosis (years, median age)	Follow-up (years, median time)	Period of treatment	RT technique	Prescribed dose to the mediastinum	Heart dose	Dose-volume predictors and clinical endpoint
Cella et al., 2011 [49]	Retrospective	56	14–70§	5.8	2002–2008	3D-CRT	32 Gy	Heart-D_{mean} 24.3 Gy* (VD) Heart-D_{mean} 22.4 Gy* (no VD)	LA-V_{25} ≥63% (OR = 5.7) and LV-V_{30} ≥25% (OR = 4.4) associated with mitral and aortic VD RV-V_{30} ≥65% (OR = 7.2) associated with tricuspid VD
Girinsky et al., 2014 [36]	Prospective	179	29	11.6	1971–2008	89% 2D-RT 11% IMRT	36 Gy	CAO-D_{mean} 33.3 Gy	CAO-D_{mean} associated with CCTA abnormalities (OR 1.13 per Gy) CCTA abnormalities found in 25% patients, a significant increase of irregularities (34%) occurred >10 years post-treatment
Cutter et al., 2015 [11]	Retrospective case control study	89 cases 200 controls	NA	18.8	1965–1995	2D-RT	25–42 Gyφ	Valve-D_{mean} 22.9-42.2 Gy♦	Approximate 30-year cumulative risks of VD: Valve-D_{mean} ≤30 Gy → 1.6% Valve-D_{mean} =31–35 Gy → 3.0% Valve-D_{mean} = 36–40 Gy → 9.3% Valve-D_{mean} >40 Gy → 12.4%
van Nimwegen et al., 2016 [20]	Retrospective case-control study	325 cases 1,024 controls	32.2	25.0	1965–1995	2D-RT	15–45 Gy•	Heart-D_{mean} 22.0 Gy* (CAD) Heart-D_{mean} 20.4 Gy* (no CAD)	↑Heart-D_{mean} associated with symptomatic AMI or angina pectoris ERR for CAD increased by 7.4% per Gy 1.74-fold increased risk at a Heart-D_{mean} of 10 Gy 2.48-fold increased risk at a Heart-D_{mean} of 20 Gy
Hahn et al., 2017 [66]	Retrospective	125	31	10.4	1988–2004	2D-RT	35 Gy♦	Heart-D_{mean} 24.9 Gy♦ Heart-D_{max} 39.1 Gy♦	Heart-D_{mean} (HR 1.09) and increasing inhomogeneity both associated with a higher risk of late cardiac effects Heart-V_{30} (HR 1.03) For ischemic events only (coronary artery model): Dose homogeneity (HR 0.94) Age (HR 1.05), LAD-V_5 (HR 0.98), LCX-V_{20} (HR 1.02)

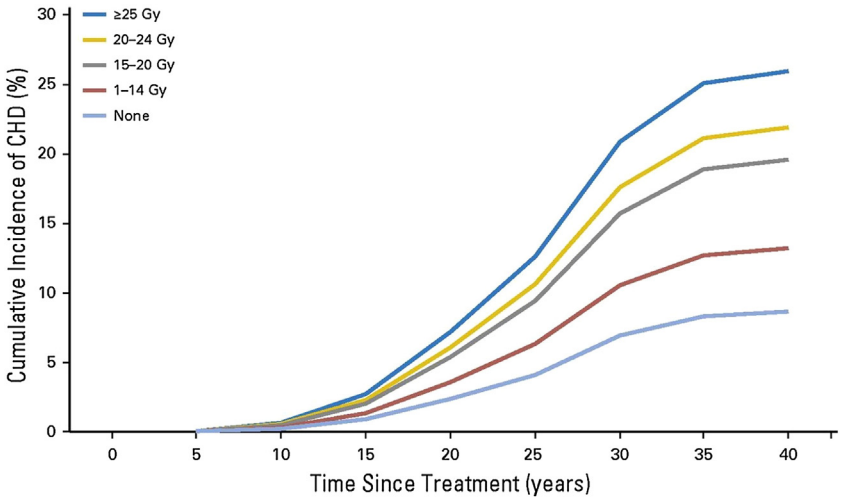

Fig. 1 – Cumulative risks of coronary artery disease (CAD) as the first cardiac event among 5-year survivors of Hodgkin Lymphoma by time since initial Hodgkin Lymphoma treatment by categories of Heart-D_{mean}. The estimated 25-year cumulative CAD incidence was 4.1%, 9.4% and 12.6% for patients with a Heart-D_{mean} of 0 Gy, 15 Gy and ≥25 Gy, respectively. Reprinted with permission. © (2016) American Society of Clinical Oncology. All rights reserved. Van Nimwegen et al.: J Clin Oncol Vol. 34 (3), Year: 2016, 235–43.

range of 1.4–6.8 Gy, there is almost no difference between the techniques when the target volume is located in the superior mediastinum (heart-D_{mean} reduction in the range of only 0–0.23 Gy).[53–56] When target volumes of the same sizes are irradiated, proton therapy, compared to photon techniques, delivers the lower absolute heart-D_{mean} (8.2 Gy vs. 10 Gy).[57]

DIBH in combination with either 3D-CRT, IMRT or even proton therapy further decreases the dose to the heart and its substructures.[55,58,59]. Mean doses to the heart, pulmonic and aortic valves, mitral and tricuspid valves and coronary arteries can be reduced by 12–15%, 20%, 30% and ≥28%, respectively.[55,59,60] The reduction is most profound in superior or inferior mediastinal target volume.[59,60] Several dosimetric studies comparing proton to photon plans have been recently conducted in lymphoma patients with mediastinal involvement.[53–57,61–63]. With proton therapy, heart-D_{mean}, heart-$V_{5–30}$ and heart wall-D_{mean} could be reduced by ≥30%,[56,61,63] left anterior descending artery, LAD-$V_{5–30}$ by 11–28%,[63] LAD-D_{mean} by 72%[54] and mean dose to the heart chambers by 47–100%.[56,61,63] In some cases, particularly in bulky mediastinal disease with anterior and posterior mediastinum involvement, proton therapy combined with DIBH, significantly reduced heart-D_{mean} to <5 Gy.[61]

Although proton therapy seems promising in reducing organ at risk (OAR) exposure to radiation and first non-randomized clinical studies, confirming low toxicity rates are available,[64] the predicted benefit of proton therapy may vary from patient to patient.[53,54,57,64] It is also associated with some disadvantages, namely possible uncertainties at the field edge, motion management, unavailability and cost of the treatment. Nevertheless, proton therapy should be reasonably considered in appropriately selected lymphoma patients, when dose to OAR can be significantly decreased.[64,65] According to the International Lymphoma Radiation Group (ILROG) recommendations, two patient groups may benefit from proton therapy in order to reduce cardiotoxicity. The first group includes patients with mediastinal disease that spans below the origin of the left main stem coronary artery and is anterior to, posterior to or on the left side of the heart and the other includes heavily pretreated patients, who are at a higher risk of radiation-related toxicity.[65]

6. Cardiotoxicity after mediastinal radiotherapy for thymic malignancies

Thymomas and thymic carcinomas are rare thoracic cancers, most often located in the upper anterior mediastinum. Indication for radiation treatment is not common in this group of tumours, but when carefully considered in the postoperative setting, typically prescribed doses are in the range of 45–50 Gy for patients with clear or close surgical margins and up to 60–70 Gy for patients with gross residual or unresectable disease.[67] In a study of thymic malignancies diagnosed in Europe between 2000 and 2007 by Siesling et al., 5-year relative survival rates for patients older than 65 and younger than 25 years were 60% and 78%, respectively.[68] Patients could be cured, and every other patient survived 15 years or more, results which should be taken into account in radiotherapy treatment planning.[69]

6.1. *Clinical and treatment planning studies*

Our search did not reveal any study correlating radiotherapy of thymoma or thymic cancer with cardiac toxicity endpoint. In a small retrospective study by Liao et al., 72 out of 130 patients with stage III thymoma received postoperative radiation treatment, with a higher heart-D_{mean} being associated with an increased risk of cardiovascular death in long-term survivors.[70] In 2018, Adams et al. published a large population-based, longitudinal cohort of 2657 patients,

treated with orthovoltage irradiation for an enlarged thymus during infancy.[71] Median estimated cumulative heart dose was 1.41 Gy (range, 0.17–202 Gy, mean 1.45 Gy), with 91% of subjects receiving <3 Gy. The authors assessed coronary heart disease events during a combined 339,924 person-years of follow-up. Estimated absorbed heart-D_{mean} <3 Gy did not increase the lifelong risk of coronary heart disease.[71]

Guidelines suggest at least 3D-CRT treatment planning to reduce the dose to OAR in the mediastinum,[67] but further improvement in dosimetric parameters was demonstrated with advanced photon techniques, such as IMRT.[72] On the other hand, particle therapy plans, with both protons and carbon ions, demonstrated lower doses to the lung, breasts, heart, oesophagus and spinal cord without compromising planning target volume (PTV) coverage when compared to 3D-CRT,[73] IMRT[74–76], VMAT[73] or helical tomotherapy, HT.[73] In a study of six patients with thymic malignancies, heart-D_{mean} was reduced on average by 36.5% (15.3 vs. 22.8 Gy, $p < 0.001$) using proton therapy compared with IMRT.[74] Vogel et al. calculated the risk of coronary events up to 20 years after radiotherapy based on mean heart doses in 22 patients treated with double-scattered proton beam therapy. Sliding-window IMRT plans were generated for all patients and compared to proton therapy plans.[76] Heart-D_{mean} (1.0 vs. 11.0 Gy, $p < 0.01$), heart-V_{30} (18 vs. 29%, $p < 0.01$), heart-V_5 (31 vs. 50%, $p < 0.01$) and left ventricle dosimetric parameters were all significantly lower with the proton therapy plans. On the other hand, LAD-D_{mean} and LAD-D_{max} did not statistically differ in both treatment methods.[76] Better heart protection finally resulted in a decreased rate of calculated major cardiac events, up to 20 years following radiation treatment (74% vs. 135%, $p = 0.04$).[76]

The DIBH technique is becoming globally available, sparing the heart high- and low-dose radiation exposure.[59,77,78] As already mentioned in the previous section, in a treatment planning study by Baues et al., the authors compared VMAT-DIBH and proton-DIBH therapy in patients with Hodgkin lymphoma. DIBH-proton combination achieved the lowest dose to the heart, lung and breasts, simultaneously with a superior target volume coverage. Dose to OAR was reduced by 38–83%.[61] A similar practice can be adopted in thymic malignancies (Fig. 2).

7. Cardiotoxicity after mediastinal radiotherapy for malignant mesotheliomas

Radiation therapy for malignant pleural mesothelioma after extrapleural pneumonectomy, pleurectomy/decortication or surgical biopsy is a real clinical challenge due to a large and circumferential PTV in order to encompass the pleural cavity. As a part of multimodality treatment in malignant mesotheliomas in (neo)adjuvant settings, prescribed doses are up to 50–60 Gy.[2,79]

7.1. *Clinical and treatment planning studies*

Feasible toxicity profiles are reported for adjuvant radiotherapy with helical tomotherapy, HT,[80–82] IMRT [83–85] VMAT[86] and recently for proton techniques.[87,88] Table 2 presents clinical studies using photon adjuvant therapy including at least some of the cardiotoxicity profile in their report.

Typical mean heart-D_{mean} doses are in the range of 18.8–24.8 Gy (VMAT), 18.5–32.9 Gy (IMRT) and 21.5–24.8 Gy (HT), with lower heart-D_{mean} in the right hemithorax radiotherapy.[90] More recently, intensity modulated proton therapy (IMPT) has been shown to be clinically safe and feasible, with increased contralateral lung, heart, esophagus, liver and ipsilateral kidney sparing compared to IMRT or VMAT photon techniques.[87,88,91,92] Clinical and comparative planning studies demonstrated clinically acceptable proton plans with simultaneous reduction of heart-D_{mean}, heart-V_{40} and V_{45} dosimetric parameters by 49–76%, 36–75% and 53–69%, respectively.[87,91,92]

A lack of prospective clinical studies and randomized controlled data in mesothelioma malignancies makes a definite conclusion regarding cardiotoxicity rather difficult. The incidence of reported grade 2 or higher cardiac events is in the range of 6–8%. Most of the presented studies are small and retrospective cohorts with a short follow-up, using different chemotherapy regimens and surgical approaches, preferably focusing only on lung toxicity with insufficient reporting on heart dosimetry. IMPT has shown promising results, particularly in limiting radiation exposure to thoracic OAR, but clinical outcomes have to be confirmed in prospective clinical trials.

8. Cardiotoxicity after craniospinal irradiation

8.1. *Clinical studies*

Clinical studies evaluating heart-related side effects of CSI in medulloblastoma patients are scarce and mostly retrospective. The prescribed total treatment dose in medulloblastoma CSI varies from 18 to 36 Gy delivered in 1.8 Gy fractions with a boost dose to intracranial or spinal metastases, when indicated.[93] It is essential to be aware of possible late treatment-related toxicity because the 5-year event-free survival rate in medulloblastoma patients is high, reaching >80%.[94] In CSI, all heart structures are susceptible to cardiac injury due to the exit radiation dose. In a small retrospective study of 19 patients treated with VMAT, heart typically received 33.5% (heart-D_{mean}) and 65.7% (heart_D_{max}) of the prescribed CSI dose. Mean dose to the PTV ranged from 18.8 to 37.9 Gy.[93] However, study follow-up was too short (≤3 years) to demonstrate any long-term cardiac sequelae. In a study by Schiopu at al., 45 patients were treated with tomotherapy CSI. The average heart-D_{mean} was 29.6% (9.2 Gy) of the absorbed PTV dose. With a median follow-up of 52 months, no acute or late cardiac toxicity was observed.[95]

8.2. *Treatment planning and risk assessment studies*

Compared to conventional 2D-RT or 3D-CRT, advanced treatment techniques (i.e., IMRT,[96] VMAT,[97,98] HT,[98,99] electron-based technique[100] and proton pencil beam scanning[101,102]) were all found to be superior regarding dosimetric parameters in order to achieve better sparing of the heart and other OAR.

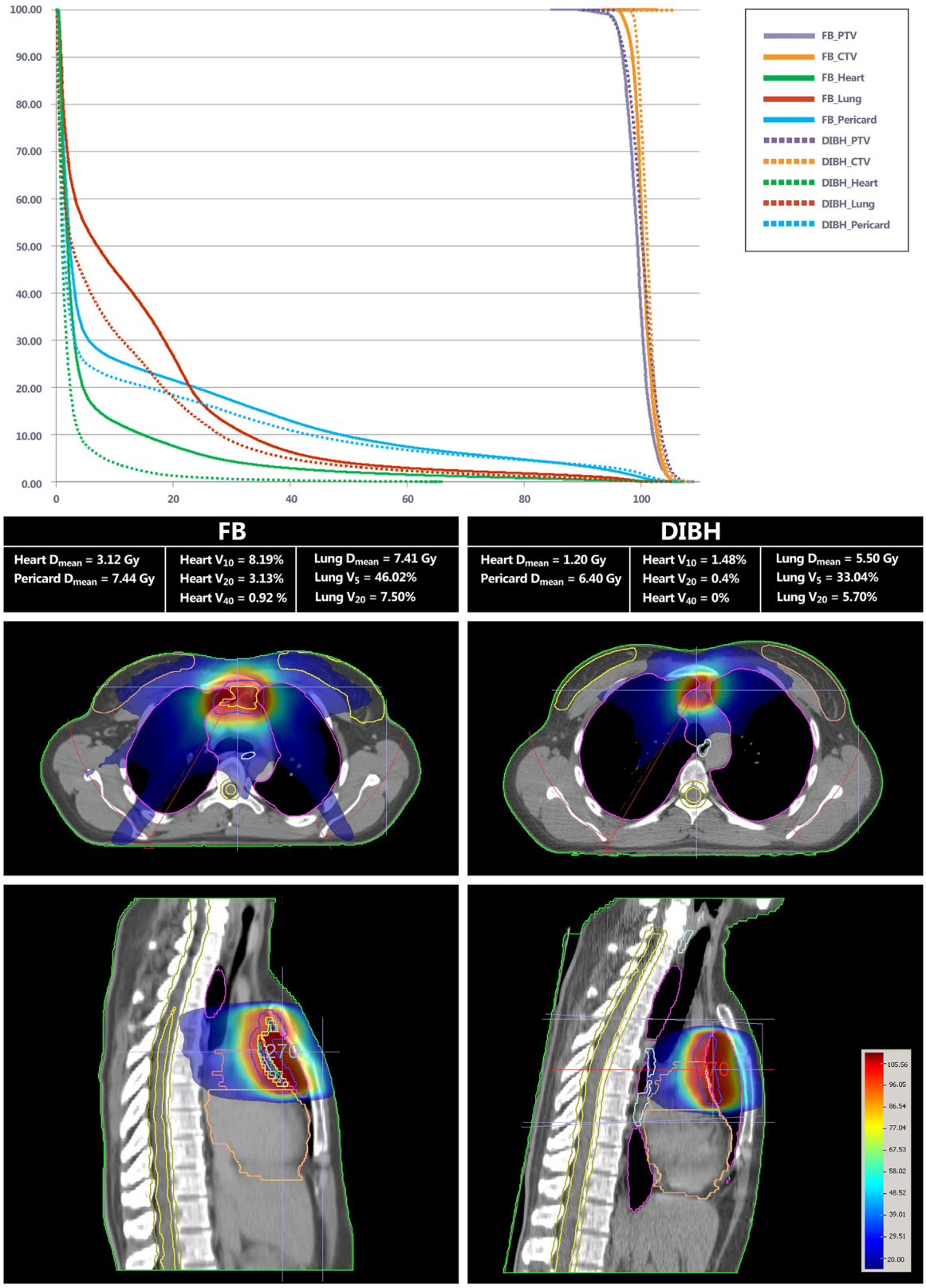

Fig. 2 – Free breathing (FB) VMAT plan and dose-volume histogram taking into account internal target motion based on 4D-CT scan versus deep inspiration breath hold (DIBH) VMAT plan in a 50-year old patient after R1 resection of thymoma.

Table 2 – Studies of adjuvant radiotherapy after surgery for mesothelioma. Abbreviations: V_x receiving at last x Gy, D_{mean}, mean absorbed dose, IMRT, intensity modulated radiation therapy, 3D-CRT, three-dimensional conformal radiation therapy, HT, Helical tomotherapy, G, grade, Gy, Gray, PTV, planning target volume.

Author and year of publication	Type of study and number of patients	Prescribed dose, target volume and radiotherapy technique	Follow-up (months, median time)	Heart absorbed dose	Cardiovascular toxicity
Rice et al., 2007 [84]	Retrospective, 63 patients after extrapleural pneumonectomy	50 or 45 Gy in 25 fractions, with a boost dose up to 60 Gy in 25 fractions IMRT (100%)	Not reported	Not reported	One (1.5%) case of death of presumed arrhythmia after receiving approximately half of the prescribed target dose Four (6%) cases of minor, self-limited cardiac events: two cases of sinus tachycardia, one new onset of atrial fibrillation and one case of mild pericarditis
Tonoli et al., 2011 [85]	Retrospective, 56 patients	50 Gy in 25 fractions with simultaneous integrated boost up to 60 Gy in 20 patients Target volume was ipsilateral hemithorax and affected mediastinum 3D-CRT (7.1%) IMRT (89.3%) HT (3.6%)	20 (range, 5–74)	Heart V_{40} = 66% and V_{50} = 14.1% (mean values)	One case of constrictive pericarditis causing death three years after radiation treatment, other cardiac toxicity not reported
Gomez et al., 2013 [89]	Retrospective, 86 patients after extrapleural pneumonectomy	45–50 Gy to the ipsilateral hemithorax and a radiation boost to 55–60 Gy when indicated IMRT (100%)	13.9 (range, 2.7–99.3)	Not reported	Six (6.9%) cases of ≥ G2 cardiac toxicity, with two (2.3%) being ≥ G3 toxicity, namely pericardial effusion and severe cardiomyopathy
Parisi et al., 2017 [80]	Retrospective, 36 patients after pleurectomy/decortication or surgical biopsy	25 Gy over 5 consecutive days, Five Gy per fraction with dose escalation up to 37.5 Gy in 26 patients HT (100%)	37.0 (range, 3.0–54.0)	Heart D_{mean}, range, 4–14 Gy	Three (8.3%), cases of pericardial effusion One (2.7%) case of pericarditis One (2.7%) case of cardiac arrest, which occurred three months following radiation treatment

Sharma et al. demonstrated clear benefits of HT regarding target volume coverage, dose homogeneity, conformity and, at the same time, OAR sparing. Heart-D_{mean}, heart-$V_{80\%}$ and $V_{10\%}$ for 3D-CRT, IMRT and HT were 17.8 Gy, 7.5 Gy, 5.0 Gy, 23.2%, 0%, 0% and 73.7%, 93.9%, 72.9%, respectively.[99]

Proton beam CSI, compared to photon beam CSI techniques, confers lower predicted healthy tissue complication risks. Due to the Bragg-peak, the exit dose to OAR in proton radiotherapy treatment delivery is considerably reduced. The estimated complication rate risk reduction is based on different models of risk assessment, as shown by Ho et al..[103] In a small study of 17 paediatric patients, the risks of cardiac mortality between field-in-field photon CSI and passively scattered proton plans were compared. The ratio of RR (proton/photon) for cardiac mortality ranged from 0.12 to 0.24. The authors were able to lower heart-D_{mean} from 10.4 ± 2.2 Gy in photon plans to 0.2 ± 0.2 Gy in reconstructed proton plans.[104] Long-term prospective clinical data are required to demonstrate clinical benefits of one radiotherapy technique over another.

9. Cardiotoxicity after total body irradiation

Long-term survivors of hematopoietic cell transplantation have an increased risk of treatment-related severe chronic health conditions, due to intense chemotherapy,[105,106] radiotherapy treatment[23,106–108] and graft versus host disease.[106,107,109] TBI itself, as part of hematopoietic cell transplantation conditioning, exposes long-term survivors to a higher risk of CVD[106–108] due to direct radiation exposure of the heart and indirect disruptions of metabolic, renal, pulmonary, neurologic and endocrine functions, causing late treatment sequelae such as growth hormone deficiency, diabetes mellitus, dyslipidaemia, metabolic syndrome, hypertension or renal failure.[106,107,110,111] In a study by Sun et al., hematopoietic cell transplantation survivors, surviving ≥10 years were 5.7 times more likely to develop a severe or life-threatening condition, such as myocardial infarction, stroke and diabetes, compared with siblings ($p < 0.001$).[109] A complete review of TBI-related heart toxicity is beyond the scope

Table 3 – Clinical studies evaluating late cardiac effects following total body irradiation as part of hematopoietic cell transplantation conditioning. Abbreviations: TBI, total body irradiation, HR, hazard ratio.

Author and year of publication	Type of study and number of patients	Prescribed dose or heart absorbed dose	Follow-up (years, median time)	Period of treatment	Age at diagnosis (years)	Cardiovascular toxicity
Van Der Pal et al., 2012 [23]	Retrospective, 1362 childhood cancer survivors 28 (10.5%) out of 266 childhood cancer survivors who received radiation treatment, received TBI	Median heart absorbed dose 15.75 Gy (range, 14.0–21.60)	22.5	1966–1996	range, 0–18	Symptomatic cardiac events, including congestive heart failure, cardiac ischemia, valvular heart disease, pericarditis and cardiac arrhythmias, were increased with anthracyclines and/or cardiac irradiation
Mulcahy Levy et al., 2013 [110]	Retrospective, 15 patients, who received TBI under three years of age	Total prescribed dose 12 Gy, delivered in six fractions of 2 Gy, lung shielded to receive less than 9 Gy, four patients received additional cranial boost irradiation to a total dose of 22 Gy	range, 1.4–13.0	1994–2010	≤3	18.2% (2 out of 11 evaluated patients) had some cardiac abnormalities, 20% (3/15) had hypertension, 69.2%, (9/13) had dyslipidaemia
Künkele et al., 2013 [112]	Retrospective, 98 paediatric cancer survivors, 39 patients included in the follow-up study	Total prescribed dose of 12 Gy, delivered in six fractions of 2 Gy, lung exposure reduced to 10 Gy	8.3 (range, 2.0–21.9)	1985–2008	17.4 (range, 7.5–30.2)	No long-term impact on cardiac function observed, defined as echocardiographic shortening fraction <30%
Marnitz et al., 2014 [113]	Retrospective, 110 patients with acute lymphoblastic leukaemia	Total prescribed dose 12 Gy, delivered in six fractions of 2 Gy; lung shielded with lung blocks, to receive less than 10 Gy	14.0 (mean time)	1985–2010	34 (mean), range, 17–54	No acute or late cardiac toxicity reported during follow-up
Novetsky Friedman et al., 2017 [107]	Retrospective, 123 childhood hematopoietic cell transplantation survivors	Total prescribed dose 12–15 Gy	8.0	1987–2011	11.8 (median), range, 1.6–21.9	Increased risk of high triglycerides and low HDL, no acute or late cardiotoxicity reported Growth hormone deficiency, history of cranial irradiation and grade II-IV acute graft versus host disease were all associated with an increased risk of developing cardiovascular risk factors
Myers et al., 2018 [114]	Retrospective cohort of two-year survivors of autologous hematopoietic cell transplantation for Hodgkin (n = 836) and Diffuse large B-cell lymphoma (n = 781) Hodgkin lymphoma: 44% (n = 371) received radiation therapy before transplantation and 5% (n = 5) received TBI Diffuse large B-cell lymphoma: 28% (n = 218) received radiation therapy before transplantation and 15% (n = 115) received TBI	Not reported	10.5 (range, 2–24.3)	1990–2008	33 (median) for Hodgkin lymphoma and 51 (median) for Diffuse large B-cell lymphoma	14 (<1%) cases of congestive heart failure 11 (<1%) cases of myocardial infarction Risk factors for overall mortality included TBI exposure in Hodgkin lymphoma ($p < 0.001$) and Diffuse large B-cell lymphoma ($p = 0.013$) survivors
Duncan et al., 2018 [115]	Multiinstitutional retrospective study of 661 two-year survivors of hematopoietic cell transplantation for childhood hematologic malignancy, 453 (83%) patients received TBI	TBI conditioning not reported Median chest irradiation dose (TBI excluded) = 7 Gy (range, 0.1–50.4) Median cranial irradiation dose (TBI excluded) = 12 Gy (range, 0.12–50.4)	8.1 (range, 2–19.2)	1995–2008	8.8 (median) range, 0.3–20.9	4.2% patients experienced at least one late cardiovascular outcome, including coronary artery disease (0.2%) cardiomyopathy (3%), cerebrovascular accident (0.6%), cardiac-related death (0.5%) The risk was increased with chest radiation (HR, 2.18, $p = 0.0087$), cranial irradiation (HR 5.58, $p < 0.0001$) and anthracycline chemotherapy (HR 4.67, $p = 0.036$) TBI was not predictive of the development of one of the primary cardiovascular outcomes

of the present work. However, we summarized published clinical data in Table 3. Reports are limited by short follow-up time, small retrospective cohorts, retrospective evaluation of cardiac events, lack of cardiac dosimetry reports, different hematopoietic cell transplantation conditioning schemes and a wide range of age at diagnosis.

10. Conclusions

Studies uniformly show a linear radiation dose-response relationship between heart-D_{mean} and the risk of dying as a result of cardiac disease, particularly when absorbed mean heart dose exceeds 5 Gy. However, cumulative incidences of CVD after mediastinal radiotherapy are low, but must be considered in the context of global increases in the number of cancer survivors. Mediastinal radiotherapy with doses of around 40 Gy with the 2D-RT technique increases the risk of cardiovascular death roughly six fold. The risk is the highest ten years post-treatment and increases with heart-D_{mean}, increasing inhomogeneity of the absorbed heart dose and depends on age at diagnosis. For specific heart substructures, only a few dose-volume predictors for cardiotoxic events are available and further studies are warranted. Asymptomatic CVD is more common and could be found at screening in the majority of lymphoma survivors, although some of these abnormalities may be of minor clinical relevance. Dosimetric studies show that the burden of cardiac toxicity is substantially reduced with modern radiotherapy techniques, compared to historical series. All efforts should be made to lower the dose to the heart and its substructures as reasonably as possible, regardless of patient age or primary tumour histology. Technological developments such as breathing control and improvements in treatment planning techniques may facilitate further reduction in cardiac mortality risks. Proton therapy is rapidly evolving and currently showing the best dosimetric advantages in sparing thoracic OAR when compared to advanced photon techniques in lymphoma, thymic malignancies, malignant mesothelioma and CSI, although real clinical benefits and cost-effectiveness have yet to be demonstrated.

Financial disclosure statements

None declared.

Conflicts of interest

None declared.

Acknowledgement

Authors would like to thank Jasna But-Hadzić, MD, Ph.D. and Rihard Hudej from Division of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia for their assistance in preparing figures for this manuscript, and David Ožura for his support with the literature search. We would like to thank Jasenka Gugić, MD, PhD, for a critical review of the article.

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