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RISK OF HEART FAILURE IN SURVIVORS OF HODGKIN LYMPHOMA: EFFECTS OF CARDIAC EXPOSURE TO RADIATION AND ANTHRACYCLINES

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Abstract

Hodgkin lymphoma (HL) survivors treated with radiotherapy and/or chemotherapy are known to have increased risks of heart failure (HF), but a radiation dose-response relationship has not previously been derived. A case-control study, nested in a cohort of 2,617 five-year survivors of HL diagnosed before age 51 years during 1965-1995, was conducted. Cases (n=91) had moderate or severe HF as their first cardiovascular diagnosis. Controls (n=278) were matched to cases on age, gender and HL diagnosis date. Treatment and follow-up information were abstracted from medical records. Mean Heart Doses (MHD) and Mean Left Ventricular Doses (MLVD) were estimated by reconstruction of individual treatments on representative computed tomography datasets. Average MLVD was 16.7 Gy for cases and 13.8 Gy for controls ($p_{difference}$=0.003). HF rate increased with MLVD: relative to 0 Gy, HF rates following MVLDs of 1-15, 16-20, 21-25 and ≥26 Gy were 1.27, 1.65, 3.84, and 4.39 respectively (p_{trend}<0.001). Anthracycline-containing chemotherapy increased HF rate by a factor of 2.83 (95%CI: 1.43-5.59), and there was no significant interaction with MLVD ($p_{interaction}$=0.09). Twenty-five year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥21 Gy were 4.4%, 6.2% and 13.3%, respectively, in patients treated without anthracycline-containing chemotherapy, and 11.2%, 15.9% and 32.9%, respectively, in patients treated with anthracyclines. We have derived quantitative estimates of HF risk in patients treated for HL following radiotherapy with or without anthracycline-containing chemotherapy. Our results enable estimation of HF risk for patients before treatment, during RT planning and during follow-up.

Introduction

With 10-year survival rates of over 80%, Hodgkin lymphoma (HL) is a model of a curable malignancy[1]. The efficacy and safety of treatments continue to improve, but late effects, including cardiovascular diseases, have caused substantial treatment-related morbidity and mortality in HL survivors treated in the past. It has been shown that mediastinal radiotherapy and/or anthracycline-containing chemotherapy increase the risk of coronary heart disease (CHD), valvular heart disease (VHD) and heart failure (HF) in HL survivors[2-9].

We previously found a linear dose-response relationship for the risk of radiation-related CHD in HL survivors with the excess rate increasing by 7.4% per Gray (Gy)[10], and a non-linear dose-response relationship for VHD, with 1.4, 3.1, 5.4, and 11.8-fold increased VHD rates for doses of ≤30 Gy, 31-35 Gy, 36-40 Gy and >40 Gy, respectively[3]. Mediastinal radiotherapy has also been associated with HF in survivors of both HL and childhood cancer[9, 11]. However, the shape of the radiation dose-response relationship has not previously been described, either for patients who received radiotherapy alone, or for patients who received radiotherapy in combination with anthracyclines. Radiotherapy use has declined but still remains an important component of HL treatment. Anthracyclines have been commonly used since the early 1980s and remain the backbone of HL chemotherapy regimens used today.

With this study, we aimed to determine the radiation dose-response relationship for HF in long-term survivors of adolescent and adult HL, to estimate cumulative risk of HF after radiotherapy given with and without anthracyclines, and to assess other determinants of HF risk.

Methods

Study population

A nested case-control study was conducted within an existing multicenter hospital-based cohort (N=2,617) of HL survivors treated in the Netherlands between 1965 and 1995 before the age of 51 years, and had survived ≥5 years after HL diagnosis. The cohort was identified through hospital-based cancer registries in four large University Hospitals and one cancer center. Over time a wide variety of treatments was used in the cohort. The majority of patients were treated

according to European Organization for Research and Treatment of Cancer Lymphoma Group protocols for primary treatment[12]. Briefly, in the 1960s patients were treated with orthovoltage therapy or cobalt-60; from the 1970s onwards, linear accelerators were used. Individual blocks were used to shield normal tissues as much as possible. Patients usually received 40 Gray (Gy) in fractions of 1.5-2.0 Gy when they were treated with radiotherapy only and 30-36 Gy when they also received chemotherapy. Mantle field irradiation (including mediastinal, axillary and neck nodes) was the most commonly applied radiation from the early 1970s to the late 1980s. Since the late 1980s, a growing number of patients received more limited radiation fields (involved fields). Treatment for recurrences was generally less standardized.

From the 1960s-1980s chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as MOPP/ABV (MOPP/doxorubicin, bleomycin, vinblastine) and ABVD (ABV and dacarbazine) were introduced as part of primary treatment. Anthracycline dose was estimated in mgs anthracycline per m2 body surface, based on number of cycles received times the standard anthracycline dose in the corresponding chemotherapy regimen during that time period. Standard doses of anthracycline per regimen per cycle were 25 mg/m2 at days 1 and 15 for ABVD and alternating MOPP-ABVD and 35 mg/m2 at day 8 for MOPP-ABV hybrid.

A detailed description of patient selection, data collection and treatments has been published previously[2, 9, 13-15], as well as assessment of cardiovascular events during follow-up[9]. Patients were eligible for this study if: a) they survived at least 5 years after HL diagnosis; b) they were diagnosed with HL before the age of 51 years; c) HL was their first primary malignancy (except for non-melanoma skin cancer, or carcinoma in situ of the cervix uteri or the breast); and d) radiotherapy for HL was the only radiotherapy given to the neck or trunk prior to the cut-off date, which was defined as date of HF for the cases, while for each control it was defined as date of HL diagnosis plus a time interval equal to the interval from date of HL diagnosis to date of HF diagnosis of the corresponding case.

Cases and controls

Cases (n=91) were patients who developed HF in the form of either symptomatic congestive HF or cardiomyopathy, with an ejection fraction (EF) of <50% (or a ≥10% drop from baseline) or a fractional shortening of <24% (based on a combination of the Common Terminology Criteria for Adverse Events versions 3.0 and 4.0: grade ≥2, see Supplemental Text 1)[16] as their first clinically significant heart disease. Cases were identified from medical records or postal questionnaires completed by the patient's general practitioner (GP)[9] and verified using cardiac notes from either the GP or the treating cardiologist. The data abstraction forms and coding instructions were developed in collaboration with physicians and it has been shown that the CTCAE can be used to properly grade cardiovascular events from medical records[17]. A total of 53 further cases of HF were excluded (see Supplemental Table 1 for reasons). Follow-up was complete to October 2013. For each case with HF, we attempted to select four controls from the cohort, individually matched on sex, age at HL diagnosis (≤1 year) and date of HL diagnosis (≤3 years). Controls had to be free of any cardiac disease grade ≥2 at the cut-off date. In total, 278 controls were matched to the cases. Cases were eligible to be controls up to the date they developed HF, and controls were selected with replacement.

Data collection

Detailed treatment information, including radiation doses and fields and cumulative chemotherapy doses, was collected from medical records. Copies of original radiotherapy prescription sheets and simulation films were obtained. Where original prescriptions were unavailable, information about radiotherapy including dates, anatomical areas, dose, fractionation and treatment energy were abstracted from other clinical notes. If cumulative chemotherapy doses were not available, regimen-specific standard doses were multiplied by the number of cycles that a patient received. Cardiotoxicity equivalence ratios of 0.50 for daunorubicin and epirubicin to doxorubicin were used[18, 19]. Vital status and dates of death were obtained up to July 2013 by linkage with the Dutch Central Bureau of Genealogy. In the Netherlands, the law requires that general practitioner and hospital records must be kept throughout a patient's lifetime and for at least 15 years after their death. Detailed data on

medical history, smoking and established cardiovascular risk factors, both at diagnosis of HL and diagnosis of HF (or cut-off date for controls) could therefore be collected for all patients from GP questionnaires in 2004 (for 94% of the cohort) and in 2013 (for 83% of the cohort), and from hospital records. In addition, a questionnaire on established cardiovascular risk factors and lifestyle was mailed to all patients in the cohort still alive in 2013 (n=475; response rate: 70%), resulting in questionnaire data for 45 cases and 186 controls. Further details are given elsewhere[2, 10, 20]. This study was approved by the ethics review board of The Netherlands Cancer Institute.

Retrospective radiation dosimetry methods

The radiation dosimetry method is described elsewhere[3]. Radiotherapy regimens were reconstructed using the Eclipse treatment planning system (TPS) (Version 13.0.28, Varian Medical System, Palo Alto, CA). Two substitute computed tomography (CT) data sets (for males and females respectively) were chosen from a library of 50 to be representative regarding average anatomy and estimated heart dose from a standardized mantle field. The heart and sub-structures of the heart were outlined as per published guidelines[21]. Treatment planning was performed for each individual patient using variables such as beam arrangement, energy, prescribed dose, field size and field shielding, which were extracted from each patient's original radiotherapy prescription charts and simulation films. Standard mantle fields, as well as para-aortic and splenic fields for patients who received such treatments, were created. The dose distributions from all fields were then summed and cardiac doses were extracted. Mean heart dose (MHD) and mean left ventricular dose (MLVD), were calculated and converted into equivalent dose in 2 Gy fractions (EQD2) and Biologically Effective Dose (BED)[22,23] When fraction size varied during treatment, EQD2 and BED were calculated separately for each fraction size before summation (see Supplemental Text 2). V20 and V30 (volume of structure receiving at least 20 or 30 Gy, respectively) were calculated for the heart and left ventricle and expressed in percentages.

For patients with neither radiation chart nor simulation film (22 cases and 103 controls), MHD and MLVD were estimated, for each combination of hospital, treatment period, sex, and radiation field, as the average value for patients with either a chart or a film.

Statistical analysis

Rate ratios (RRs) for HF for different levels of each factor were estimated using logistic regression, conditional on sets of individual cases and their matched controls. Confidence intervals (CIs) for factors with two levels were based on the Wald method. CIs for factors with >2 levels used the amount of information in each category, including the reference category[24]. Multiple regression was used to control for confounding and to assess the combined effect of radiation dose and other factors. The dose-response was estimated by modelling HF rate as $K_m(1+\beta d)$ where d is radiation dose, K_m is a constant specific to each matched set and β is the increase in excess HF relative rate per unit increase in dose. Nonlinearity was evaluated by including an exponential term: $K_m[1+\beta d \cdot \exp(\delta d)]$ and goodness of fit assessed by likelihood ratio tests. Approximate cumulative risks of HF for categories of radiation dose were estimated from the HF rate ratios together with the cumulative risk of HF for the entire cohort (Supplemental Text 3). Significance tests were two-sided and $p \leq 0.05$ was taken to indicate statistical significance. Analyses were performed using STATA statistical software version 13.0 (STATAcorp 2013)[25] and Epicure version 1.8 (Hirosoft International)[26].

Results

In the 91 cases, HF occurred after a median interval of 20.6 years (interquartile range (IQR): 13.7-25.2) (Table 1). The majority of HF diagnoses were grade 2 (44%) or 3 (43%) (Supplemental Table 1). The median age at HL diagnosis was 28.3 years (IQR: 21.9-37.7). Fifty-seven percent of the HF cases had died by the end of follow-up, with median time from HF to death of 3.6 years (IQR: 0.2-5.6).

Radiotherapy, chemotherapy and splenectomy

For patients given mediastinal radiotherapy (cases 90.1%, controls: 82.3%; $p_{difference}$ =0.078), the average prescribed dose was 30.5 Gy (cases: 32.7 Gy, controls 29.8 Gy, $p_{difference}$=0.088), while the average MHD was lower at 20.9 Gy (cases: 23.2 Gy, controls: 20.1 Gy, $p_{difference}$=0.009), and the average MLVD even lower, at 14.5 Gy (cases: 16.7 Gy, controls: 13.8 Gy, $p_{difference}$=0.003). MHD and MLVD were strongly correlated (correlation coefficient: 0.93, Supplemental Figure 1).

For all three measures of dose, HF rate increased with increasing dose (prescribed mediastinal dose: p_{trend}=0.027, MHD: p_{trend}=0.002, MVLD: p_{trend}<0.001; Table 2). For MHD, the dose-response relationship was non-linear ($p_{curvature}$=0.029, Supplemental Table 2), with little evidence of an increase for MHDs in the range 1-25 Gy, but increasing steeply with MHDs of ≥25 Gy (Figure 1, left panel). For MLVD, there was no significant departure from linearity ($p_{curvature}$=0.09) (Figure 1, right panel). HF rate also increased with increasing V30 and V20 for the left ventricle (Table 2). When the analysis was repeated omitting patients with neither radiation chart nor simulation film, results were similar (Supplemental Table 3 and Supplemental Figure 2).

Chemotherapy without anthracyclines was not significantly associated with HF (RR: 0.93, 95%CI: 0.63-1.37). However, for anthracycline-based chemotherapy, the HF rate was increased by a factor of nearly three (RR: 2.83, 95%CI: 1.43-5.59). Among those who received anthracyclines, HF rates were similar for those with cumulative doses <280 mg/m^2 and those with cumulative doses ≥280 mg/m^2 ($p_{difference}$=0.97). HF rates were similar among those with and without splenectomy (RR: 0.85, 95% CI: 0.49-1.45). Among those who received mediastinal RT as primary therapy, HF rates did not differ significantly between those who received anthracyclines only as primary therapy, and those who received anthracyclines only as salvage therapy (RR: 2.30, 95% CI 1.02-5.21 versus RR: 3.85, 95% CI 1.59-9.36, $p_{difference}$=0.4) (Table 2). Only two patients received anthracyclines for primary as well as salvage treatment; both were cases.

HF rate-ratios in individuals with MHD or MLVD ≥26 Gy relative to 0-25 Gy did not differ significantly according to use of anthracycline chemotherapy ($p_{interaction}$=0.45 for MHD, 0.09 for MLVD) or with splenectomy ($p_{interaction}$=0.71 for MHD, 0.62 for MLVD).

Classical cardiovascular disease risk factors

None of the known classical cardiovascular disease risk factors differed significantly between HF cases and matched controls. Diagnosis of diabetes mellitus between HL and cut-off was associated with a non-significantly increased HF rate (RR: 1.59, 95% CI 0.63-4.05) compared to those not diagnosed with the disease (Supplemental Table 4). When taking into account all risk factors that were diagnosed before the end of follow-up, instead of only those diagnosed prior to HF/cut-off date, hypertension (RR: 1.80, 95%CI: 0.73-4.44), diabetes mellitus (1.83, 95%CI: 0.96-3.47) and having at least one risk factor (RR: 1.53, 95%CI: 0.93-2.52) were all associated with non-significantly increased HF rates, while patients with a high level of physical activity (≥3 hours per week) at time of follow-up had a non-significantly lower HF rate than those who were not (<1 hour per week) (RR: 0.59, 95%CI: 0.32-1.10).

HF rate-ratios in individuals with MHDs or MLVDs ≥26 Gy relative to 0-25 Gy did not differ significantly according to presence of at least one cardiovascular risk factor, gender, age at HL diagnosis, or time since HL diagnosis (all $p_{interaction}$ values >0.50 - see Supplemental Tables 5A and 5B).

Estimated heart failure rates and cumulative risks

Our analyses showed that the only factors significantly associated with HF rate were radiation dose and whether or not anthracyclines were used, with no significant multiplicative interaction between the two. Summary HF rates were therefore estimated based on three broad categories of MHD or MLVD and whether or not anthracyclines had been given, with the assumption that the multiplicative increase in HF rate with anthracyclines did not differ according to MHD or MLVD (Table 3). Based on these estimates, approximate cumulative incidence curves for HF were derived for patients in these six groups (Figure 2). In patients treated without anthracyclines, 25-year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥21 Gy were 4.4%, 6.2% and 13.3%, while in patients treated with anthracyclines the 25-year cumulative risks were 11.2%, 15.9% and 32.9%, respectively. For patients treated without anthracyclines, 35-year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥21 Gy were 7.2%, 10.2%, 21.8%, respectively. Patients treated with anthracyclines have not yet been followed for long enough to estimate risks beyond 25 years.

Discussion

In this study we have examined, for the first time, dose-response relationships for HF rate based on cardiac radiation exposure in 5-year survivors of adolescent or adult HL. We conducted analyses based on estimates of both MHD and MLVD derived from individual radiotherapy plans. Both measures of dose suggested that there is little increase in HF risk for lower doses – up to 25 Gy MHD or up to 15 Gy MLVD – but that HF rates increase rapidly at higher doses. We also found that treatment with anthracyclines increase the HF rate, approximately 3-fold, irrespective of cardiac radiation exposure.

A radiation dose-response relationship for self-reported HF has previously been observed in the Childhood Cancer Survivor Study (CCSS)[11, 27]. In that cohort, HF risk was increased by factors of 1.6, 3.1 and 10.5 following MHDs of 5-14, 15-34 and ≥35 Gy respectively, compared with patients who did not have any cardiac radiation exposure[27]. These proportional increases are somewhat higher than those in our present study, possibly due to the patients' younger ages at cancer treatment: 82.4% of the CCSS cohort were aged less than 15 years at cancer diagnosis compared with only 3.5% in the present study. A clearly increasing HF risk with increasing anthracycline dose was also seen in the CCSS study, and risk was increased by factors of 2.1, 3.7 and 10.5 for cumulative anthracycline doses of <100, 100-249, and ≥250 mg/m^2 compared with those not exposed to anthracyclines.

In the CCSS, the therapy-associated risk of HF was potentiated by the presence of cardiovascular risk factors such as hypertension and diabetes mellitus, and by lack of physical activity[28, 29]. In our current study, no such associations were apparent. However, the CCSS studies were based on patient-reported outcomes of cardiovascular risk factors, and probably also included risk factors diagnosed at the same time as or even after the cardiovascular disease of interest, possibly resulting in an overestimation of the strength of the associations. In contrast, our conservative approach of including only risk factors diagnosed prior to HF, may have resulted in an underestimation. Despite this, it seems likely that risk factor control in high-risk patients who received cardiotoxic treatment may be important in risk-reduction strategies for cardiovascular diseases after HL treatment.

The strengths of our study include that it was performed in a complete, multi-institutional population with long-term, detailed follow-up, including information from cardiologists and GPs. The outcome (HF) was GP-reported and, if necessary, confirmed by cardiologists, which is an important advantage in comparison with studies relying on patient-reported outcomes or registry data[6, 30-32]. Instead of using prescribed radiation dose, radiation-related HF risks were estimated using individual patient dosimetric parameters such as MHD and MLVD, which were converted into EQD2 and adjusted for dose distribution and varying fractionation schedules. Where available, individual cumulative anthracycline doses were analyzed, rather than protocol prescription chemotherapy doses.

A limitation of our study is that a total of only 90 patients were prescribed anthracyclines, all but 11 of whom also received mediastinal radiotherapy. Furthermore, the range of cumulative anthracycline doses was limited, with most patients being prescribed either 280 or 300 mg/m2 doxorubicin equivalent, and follow-up for patients who received anthracyclines was shorter than for patients treated with radiotherapy alone. Therefore, our ability to study the interaction between radiation exposure of the heart and anthracycline exposure was limited, and we were unable to estimate a separate dose-response relationship for anthracyclines.

The results indicate that salvage therapy with anthracyclines following primary treatment with mediastinal radiotherapy would be more harmful than primary treatment with mediastinal radiotherapy and anthracyclines. However, the small number of patients treated with anthracyclines makes it impossible to draw any firm conclusions regarding the possible effect of the time elapsed between exposure of the heart to anthracyclines and to radiation. It is hypothesized that this increased risk is associated with an increased radiation dose during primary treatment, and perhaps an increased anthracycline dose for salvage treatment, compared to the doses for combined primary treatment. Further research may indicate whether treatment sequence may influence HF risk, which may contribute to risk prediction models of cardiovascular disease in survivors who have been treated in the past.

Detailed radiotherapy information was collected for each patient, but radiotherapy was applied before the era of CT-based treatment planning. Dose reconstructions were therefore

carried out using representative CT datasets, and these cannot take into account patient-specific variations in heart size, shape and position. For a proportion of patients, both the radiotherapy chart and the simulation film were missing and the MHD and MLVD were estimated rather than reconstructed (see Methods). However, a sensitivity analysis including only patients for whom MHD and MLVD were reconstructed, showed similar results (see Supplemental Table 3 and Supplemental Figure 2). Our study includes only cases for whom HF was the first cardiovascular diagnosis, in order to eliminate the effects of other cardiovascular diseases such as CHD or VHD on the risk of developing HF. However, in a previous study[9], we showed that HF occurred frequently subsequent to CHD or VHD, rather than as a first event. Additional research is needed to study the influence of previous cardiovascular diseases and to identify risk factors for developing multiple cardiovascular diseases.

For patients treated today, MHDs and MLVDs will usually be well below the average values of 20.9 Gy and 14.5 Gy reported in this study, due to reductions in both treatment volumes and prescribed doses. Involved field radiotherapy has been reported to give a median MHD of 17.2 Gy for prescribed doses of 35 Gy and involved node radiotherapy leads to even lower doses (median MHDs of 7.7-12.0 Gy for prescribed doses of 36 Gy)[33-35]. Also, anthracycline doses are nowadays frequently lower than the doses received by the majority of patients in our study. Therefore, patients treated today are likely to be at a substantially lower risk of treatment-related HF than the patients included in this study. Studies in larger populations of HL survivors treated more recently would be helpful in characterizing the risks from modern treatments more precisely. More accurate dosimetry based on a patient's individual CT scan may also help to determine whether MHD, MLVD or another dosimetric parameter is the best measure to predict radiation-related HF risk. However, in the absence of more precise measures, these dose-response relationships for MHD and MLVD can be used to estimate HF risk both in patients treated today, and in survivors treated in more recent decades.

In conclusion, cardiac radiation exposure and treatment with anthracyclines are important risk factors for the development of HF in HL survivors. Our findings are important for clinicians to provide information regarding risks of HF before treatment, during radiation

treatment planning and during long-term follow-up of HL survivors, including patients treated in the past.

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Disclosures:

The authors declare no conflicts of interest.

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Table 1: Characteristics of cases and controls

	Cases		Controls	
	N	%	N	%
Total	91	100%	278	100%
Sex[¥]				
Males	47	51.6%	139	50.0%
Females	44	48.4%	139	50.0%
Age at HL diagnosis[¥]				
Median age (IQR) in years	28.3	(21.9-37.7)	28.2	(22.9-37.7)
5-25 years*	38	41.8%	107	38.5%
26-35 years	24	26.4%	86	30.9%
36-50 years	29	31.9%	85	30.6%
Age at HF diagnosis/cut-off date				
Median age (IQR) in years	47.9	(41.2-57.7)	48.2	(41.5-57.6)
27-40 years	21	23.1%	59	21.2%
41-60 years	42	46.1%	127	45.7%
≥61 years	28	30.8%	92	33.1%
Year of diagnosis HL diagnosis[¥]				
1965-1974	30	33.0%	98	35.3%
1975-1984	35	38.5%	114	41.0%
1985-1995	26	28.6%	66	23.7%
Time to HF diagnosis/cut-off date				
Median time (IQR) in years	20.6	(13.7-25.2)	20.6	(14.0-25.0)
5-10 years	14	15.4%	43	15.5%
11-20 years	33	36.3%	101	36.3%
21-30 years	38	41.8%	121	43.5%
≥31 years	6	6.6%	13	4.7%
Deceased at end of follow-up				
Median time (IQR) in years after cut-off	3.6	(0.2-5.6)	8.2	(4.6-14.4)
No	39	42.9%	171	61.5%
Yes	52	57.1%	107	38.5%

HL: Hodgkin lymphoma; HF: heart failure; IQR: Interquartile range

[¥] matching variables used in the selection of controls

**4 cases and 9 controls (3.5% of the population) were aged <15 years at time of HL diagnosis*

Table 2: Associations between treatment and HF risk

Treatment factor	Cases (total: 91)		Controls (total: 278)				
	N	%	N	%	RR*	95%CI	p_{trend}^
Radiotherapy							
No RT to mediastinum or PAO	7	7.7	33	11.9	1.00	0.40-2.50	
PAO-RT, no mediastinal RT	2	2.2	16	5.8	0.66	0.15-2.98	
Mediastinal RT, no PAO-RT	39	42.9	126	45.3	1.87	1.27-2.75	
Mediastinal RT & PAO-RT	43	47.2	103	37.0	2.59	1.80-3.72	0.020
Prescribed mediastinal dose							
Average (SD)	32.7	(12.2)	29.8	(14.6)			
Median (IQR)	37	(32-40)	36	(30-40)			
0 Gy (no mediastinal RT)	9	9.9	49	17.6	1.00	0.45-2.23	
20-34 Gy (median 32 Gy)	15	16.5	45	16.2	2.35	0.85-6.46	
35-39 Gy (median 36 Gy)	34	37.4	113	40.7	2.10	0.86-5.13	
≥40 Gy (median 40 Gy)	33	36.3	71	25.5	3.02	1.23-7.40	0.027
Mean heart dose (MHD)							
Average (SD)	23.2	(9.6)	20.1	(10.0)			
Median (IQR)	25.8	(18.8-30.0)	22.5	(16.7-27.2)			
0 Gy	7	7.7	29	10.4	1.00	0.39-2.55	
1-20 Gy (median 16 Gy)	21	22.2	70	24.4	1.43	0.83-2.50	
21-25 Gy (median 23 Gy)	20	22.2	102	37.1	1.03	0.63-1.67	
26-30 Gy (median 28 Gy)	27	30.0	57	20.7	2.78	1.69-4.59	
≥31 Gy (median 33 Gy)	16	17.8	20	7.3	4.16	2.14-8.10	0.002†
Mean dose to the left ventricle (MLVD)							
Average (SD)	16.7	(8.8)	13.8	(7.9)			
Median (IQR)	16.5	(11.9-21.9)	15.1	(8.4-19.1)			
0 Gy	7	7.7	29	10.4	1.00	0.39-2.55	
1-15 Gy (median 13 Gy)	36	39.5	144	51.8	1.27	0.86-1.89	
16-20 Gy (median 19 Gy)	20	22.0	68	24.5	1.65	0.98-2.77	

21-25 Gy (median 23 Gy)		16	17.6	23	8.3	3.84	1.97-7.47	
≥26 Gy (median 30 Gy)		12	13.2	14	5.1	4.39	2.00-9.65	<0.001†
V30 for the left ventricle (%)¶								
Average (SD)		40.8	(24.7)	33.9	(23.7)			
Median (IQR)		42.8	(24.8-54.7)	40.1	(13.1-49.4)			
0%		9	9.9	35	12.6	1.00	0.48-2.10	
1-24% (median 12%)		17	18.7	60	21.6	0.95	0.52-1.71	
25-49% (median 40%)		33	36.3	121	43.5	1.05	0.70-1.58	
50-74% (median 60%)		23	25.3	51	18.3	1.80	1.12-2.91	
75-100% (median 84%)		9	9.9	11	4.0	3.22	1.32-7.86	0.021†
V20 for the left ventricle (%)¶								
Average (SD)		49.2	(26.3)	41.6	(26.4)			
Median (IQR)		53.2	(33.3-63.3)	48.5	(26.9-57.2)			
0%		8	8.8	32	11.5	1.00	0.45-2.23	
1-24% (median 5%)		4	4.4	33	11.9	0.27	0.06-1.11	
25-49% (median 39%)		28	30.7	87	31.3	1.38	0.89-2.14	
50-74% (median 58%)		35	38.5	98	35.3	1.51	0.99-2.28	
75-100% (median 86%)		16	17.6	28	10.1	2.50	1.33-4.69	0.006†
Chemotherapy								
No chemotherapy		23	25.3	82	29.5	1.00	0.65-1.55	
CT, but no anthracyclines		37	40.6	137	49.3	0.93	0.63-1.37	
CT with anthracyclines		31	64.1	59	21.2	2.83	1.43-5.59	0.043
Cumulative anthracycline dose¥								
0 mg/m^2		60	65.9	219	78.8	1.00	0.57-1.74	
<280 mg/m^2 (median 210mg/m^2)		7	7.7	12	4.3	2.99	1.05-8.50	
≥280 mg/m^2 (median 300mg/m^2)⊕		24	26.4	47	16.9	2.93	1.30-6.59	0.006‡
Salvage therapy								
Primary therapy	Salvage therapy							
Mediastinal RT, no anthra	None or no anthra	51	56.0	170	61.2	1.00	0.67-1.47	
Mediastinal RT, anthra	None or no anthra	13	14.3	31	11.2	2.30	1.02-5.21	
Mediastinal RT, no anthra	Anthra	12	13.2	14	5.0	3.85	1.59-9.36	

Other°	Other°	15	16.5	63	22.7	0.59	0.31-1.14	
Splenectomy								
	No	60	66.7	176	63.8	1	ref	
	Yes	30	33.3	100	36.2	0.85	0.49-1.45	0.54
	Unknown	1	1.1	2	0.7	-	-	

Note: MHDs and MLVDs are EQD2 Gy (see Methods). Treatment variables include both primary and salvage treatment. RT: radiotherapy; PAO: para-aortic; SD: standard deviation; IQR: Interquartile range; RR: rate ratio; CT: chemotherapy; anthra: anthracyclines

*RRs were estimated conditionally on the matched sets

[ℵ]Trend test based on median value of the treatment factor in each category

†p_{trend} after adjusting for treatment with anthracyclines: mean heart dose <0.001, mean dose to the left ventricle 0.001, V30 of the left ventricle 0.034, V20 of the left ventricle 0.006.

‡ P_{trend} after adjusting for mean heart dose 0.011; after adjusting for mean dose to the left ventricle 0.015.

[¶]V30 and V20 are the percentages of the left ventricle volume that received at least 30 and 20 Gy respectively

[¥] 6 cycles of MOPP-ABV hybrid contain 210mg/m^2 anthracycline (35 mg/m^2 per cycle); 6 cycles of ABVD contain 300 mg/m^2 anthracycline (50mg/m^2 per cycle). There was no significant difference between the HF rate in the two dose categories <280 mg/m^2 and ≥280 mg/m^2 (p=0.97).

[⊕] Most patients who received anthracyclines received either 6 ABVD (prescribed anthracycline dose 300mg/m^2) or 8 MOPP-ABV hybrid (prescribed anthracycline dose 280mg/m^2)

[°] Includes mainly patients who did not receive mediastinal RT at all, or received mediastinal RT only for salvage treatment, or received anthracyclines for both primary and salvage treatment

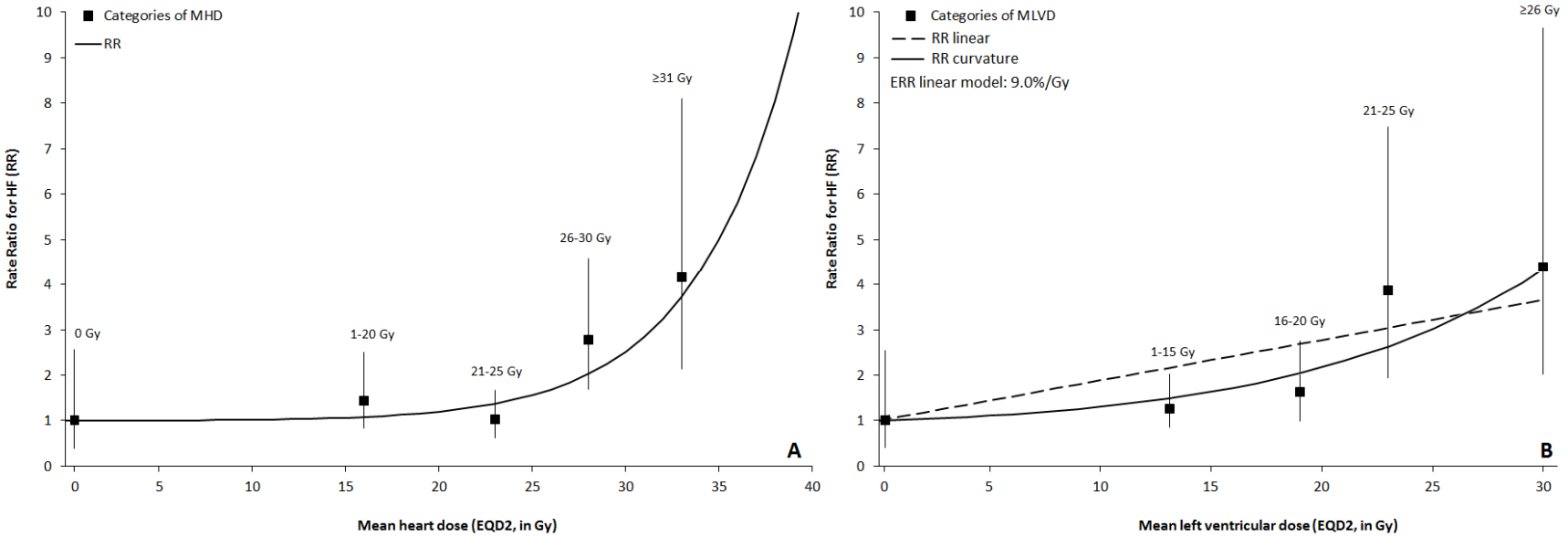
Table 3: Estimated heart failure rates by radiotherapy dose and anthracycline treatment*

	Treated without anthracyclines				Treated with anthracyclines			
	#cases	#controls	RR	95%CI	#cases	#controls	RR	95%CI
Mean heart dose (EQD2)								
0-25 Gy	28	153	1.00	0.67-1.48	20	48	**2.92**	1.35-6.30
26-30 Gy	22	49	**2.43**	1.51-3.91	5	8	**7.09**	2.56-19.67
≥31 Gy	10	17	**3.67**	1.86-7.25	6	3	**10.71**	3.51-32.67
Mean left ventricular dose (EQD2)								
0-15 Gy	26	133	1.00	0.68-1.47	17	40	**2.60**	1.21-5.58
16-20 Gy	17	60	**1.43**	0.85-2.44	3	8	**3.74**	1.31-10.73
≥21Gy	17	26	**3.10**	1.87-5.14	11	11	**8.06**	3.05-21.32
V30 left ventricle (%)								
0-24%	9	51	1.00		4	16	**3.36**	1.57-7.22
25-100%	51	168	**2.57**	1.25-5.29	27	43	**8.65**	2.83-26.41
V20 left ventricle (%)								
0-49%	26	118	1.00		14	34	**2.84**	1.36-5.97
50-100%	34	101	**1.58**	0.94-2.67	17	25	**4.50**	1.85-10.98

RR: Rate ratio; EQD2: equivalent dose in fractions of 2 Gray; V20/V30: volume of the structure that received at least 20/30 Gray

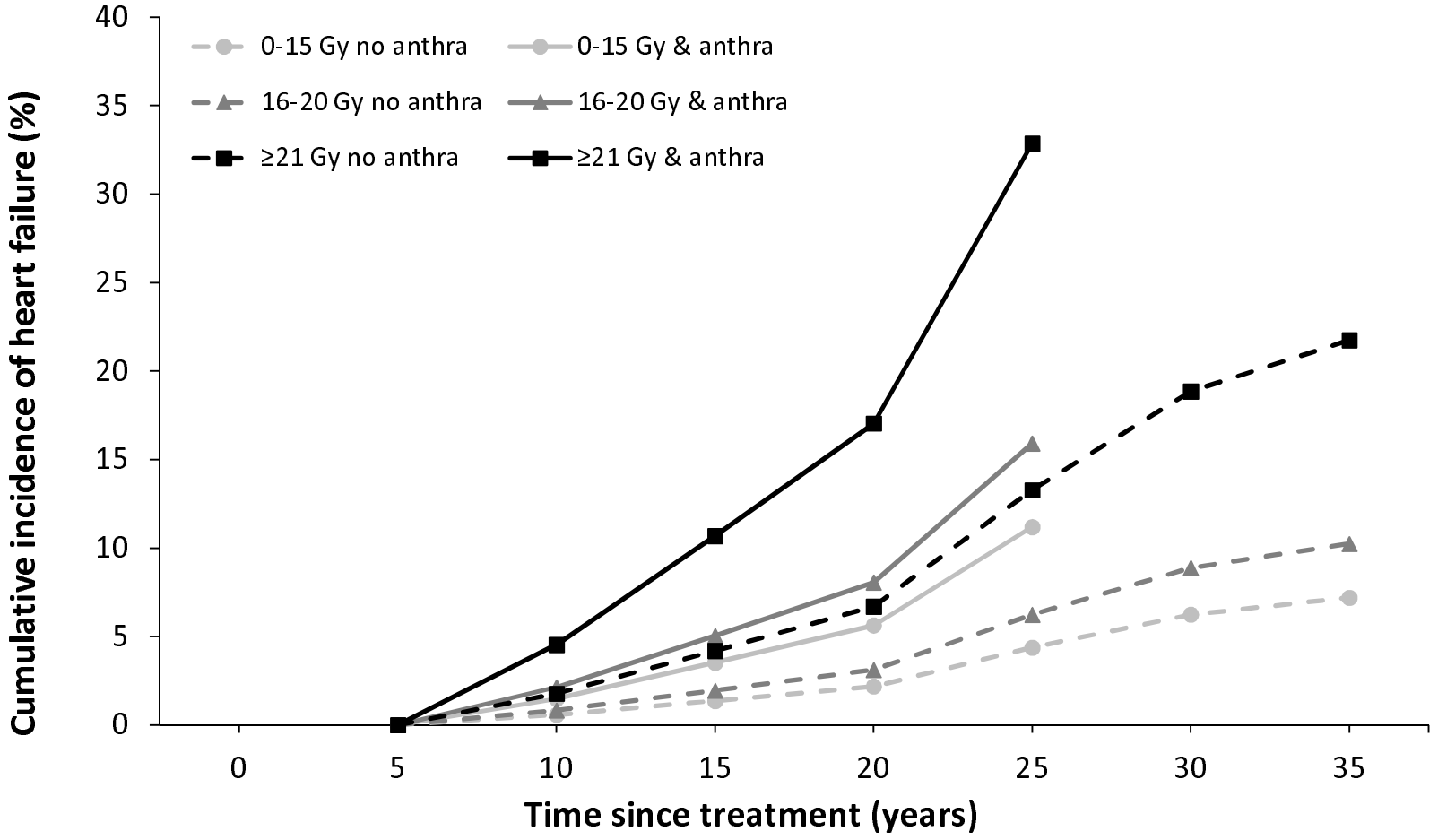
*There was no significant interaction on a multiplicative scale between anthracycline treatment and either mean heart dose or mean left ventricular dose (see Supplemental Tables 5A &5B). Therefore, estimates of heart failure rates by radiotherapy dose and anthracycline treatment were calculated under the assumption that there was no multiplicative interaction between the two. Estimates allowing for an interaction between radiotherapy dose and anthracycline treatment are given in Supplemental Table 6.

Figure 1: Relationship between heart failure rate and cardiac dose*



*Rate ratios (RRs) for heart failure (HF) by mean heart dose (left panel) and by mean left ventricular dose (right panel) in Gy compared with no radiation exposure. RRs are calculated conditionally on matched sets after adjustment for anthracycline-based chemotherapy (yes/no). Squares indicate anthracycline-adjusted estimates for the following dose categories: mean heart dose: 0 Gy, 1-20 Gy, 20-25 Gy, 26-30 Gy, ≥31 Gy; mean left ventricular dose: 0 Gy, 1-15 Gy, 16-20 Gy, 21-25 Gy, ≥26Gy, and are plotted at the median dose in each category (0 Gy, 16 Gy, 23 Gy, 28 Gy, and 33 Gy for mean heart dose; 0 Gy, 13 Gy, 19 Gy, 23 Gy, and 30 Gy for mean left ventricular dose). Vertical lines are 95% confidence intervals. For mean heart dose, there was a statistically significant linear dose-response relationship (p=0.006) and allowing for curvature improved the fit significantly (p=<0.001). For mean left ventricular dose, there was a statistically significant linear dose-response relationship (p=0.004) and allowing for curvature did not significantly improve the fit (p=0.09). Further details are given in Supplemental Table 2.

Figure 2: Approximate cumulative risks of HF by mean left ventricular dose and whether or not treatment with anthracyclines was given*



* Modelled cumulative risk of heart failure (HF) as first cardiac event among five-year survivors of Hodgkin lymphoma (HL) by time since initial HL treatment for categories of mean left ventricular dose (Gy). Lines indicate estimated cumulative incidences for dose categories (0-15 Gy, 16-20 Gy and ≥21 Gy) with and without anthracycline exposure. Cumulative risks were calculated with other heart disease or death as a competing risk. Further details are given in Supplemental text 3.

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Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines

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