Late cardiotoxicity after treatment for Hodgkin lymphoma

Berthe M. P. Aleman,[1] Alexandra W. van den Belt-Dusebout,[2] Marie L. De Bruin,[2] Mars B. van 't Veer,[3] Margreet H. A. Baaijens,[4] Jan Paul de Boer,[5] Augustinus A. M. Hart,[1] Willem J. Klokman,[2] Marianne A. Kuenen,[2] Gabey M. Ouwens,[2] Harry Bartelink,[1] and Flora E. van Leeuwen[2]

[1]Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Department of Hematology, the Dr Daniel den Hoed Cancer Center, Rotterdam, The Netherlands; [4]Department of Radiotherapy, the Dr Daniel den Hoed Cancer Center, Rotterdam, The Netherlands; [5]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

We assessed cardiovascular disease (CVD) incidence in 1474 survivors of Hodgkin lymphoma (HL) younger than 41 years at treatment (1965-1995). Multivariable Cox regression and competing risk analyses were used to quantify treatment effects on CVD risk. After a median follow-up of 18.7 years, risks of myocardial infarction (MI) and congestive heart failure (CHF) were strongly increased compared with the general population (standardized incidence ratios [SIRs] = 3.6 and 4.9, respectively), resulting in 35.7 excess cases of MI and 25.6 excess cases of CHF per 10 000 patients/year. SIRs of all CVDs combined remained increased for at least 25 years and were more strongly elevated in younger patients. Mediastinal radiotherapy significantly increased the risks of MI, angina pectoris, CHF, and valvular disorders (2- to 7-fold). Anthracyclines significantly added to the elevated risks of CHF and valvular disorders from mediastinal RT (hazard ratios [HRs] were 2.81 and 2.10, respectively). The 25-year cumulative incidence of CHF after mediastinal radiotherapy and anthracyclines in competing risk analyses was 7.9%. In conclusion, risks of several CVDs are 3- to 5-fold increased in survivors of HL compared with the general population, even after prolonged follow-up, leading to increasing absolute excess risks over time. Anthracyclines further increase the elevated risks of CHF and valvular disorders from mediastinal radiotherapy. (Blood. 2007; 109:1878-1886)

Introduction

Over the past decades, survival of patients treated for Hodgkin lymphoma (HL) has improved dramatically, as a result of the development of multiagent chemotherapy (CT), more accurate radiotherapy (RT), and enhanced possibilities to reduce treatment complications.[1] Unfortunately, the improved prognosis of HL has been accompanied by long-term toxicity, such as elevated risks of second primary malignancies,[2-9] cardiovascular disease (CVD),[2,3,8-10] and infections.[2,8,9] Increased mortality of cardiac disease after mediastinal radiotherapy for HL has been reported in several studies.[2,3,8-10] Dose-dependent anthracycline-induced cardiotoxicity has been observed in survivors of malignancies other than HL, who were usually treated with higher anthracycline doses.[11,12] It is not known, therefore, whether anthracyclines add to the increased risk of CVD from mediastinal RT for survivors of HL. This is an important clinical question because most patients with HL now receive anthracycline-containing chemotherapy. Although a few studies reported on nonfatal cardiac events, comparisons with the general population were usually not made, because in most countries CVD incidence rates are not available.[13-18] The purpose of our study was to assess the long-term risk of various CVDs in a cohort of 1474 five-year survivors of HL treated between 1965 and 1995.

Unique features of this study include long and near complete follow-up and the availability of complete treatment data, including radiation fields and chemotherapeutic agents. In addition, we compared the incidence of various CVDs with population-based reference rates from the general population, we accounted for competing risk of death from any cause, and we incorporated cardiac risk factors in the analyses.

Patients and methods

Data collection procedures

We included all 5-year survivors of HL diagnosed before age 41 years (n = 1486) from our late-effects HL cohort comprising 2689 patients with HL as the first malignancy.[6,9,19] Patients were treated between 1965 and 1995 and identified through the hospital-based cancer registries of The Netherlands Cancer Institute, Amsterdam, or the Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam. Patient selection and methods of data collection have been described in detail previously.[6,9,19] Data were collected on date of birth, date of HL diagnosis, histology, clinical stage, cytostatic agents in primary and salvage treatment, radiation fields in primary and salvage treatment, dates and treatments of relapses, dates of diagnoses of cardiovascular events, cardiovascular risk factors at HL diagnosis and at end of follow-up, date of most recent medical information or date of death, vital status, and cause of death. Smoking was scored positive when the patient was smoking at the end of follow-up or had stopped smoking less than 1 year before the end of follow-up. Hypertension, hypercholesterolemia, and diabetes mellitus were scored positive when stated in the medical information or when treated. Data were collected directly from the medical records, through general practitioners (GPs) and attending physicians.

Submitted July 12, 2006; accepted October 4, 2006. Prepublished online as *Blood* First Edition Paper, November 21, 2006; DOI 10.1182/blood-2006-07-034405.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Questionnaires on specific cardiovascular diagnoses and risk factors were sent to the patients' GPs and/or the patients' last known attending physicians in case the information could not be obtained from the medical record. When there was ambiguous information on CVDs, additional information was requested from the patient's cardiologist (n = 43). Patients were not routinely screened for CVDs. For patients who died from acute CVD, without prior evidence of preceding CVDs, date of death was recorded as date of diagnosis of CVD and cause of death as CVD diagnosis.

Twelve patients were excluded from the original cohort, because medical records could not be obtained and no information on CVD was received from the GP, leaving 1474 patients for analysis.

Treatment

Patients were usually treated in or according to EORTC trials.[20] The distribution of radiotherapy fields is given in Table 1 and Figure 1, based on individual treatment data. Radiotherapy techniques have changed over the years. In the 1960s, patients were treated with cobalt-60 or orthovoltage therapy; from the 1970s onward, linear accelerators were used (usually 8 MV photons). Individual blocks were used to shield normal tissues as much as possible. Shielding of the distal part of the mediastinum was sometimes performed from the late 1980s onward in case there was no spread of disease below the aortic notch. The vast majority of mediastinally irradiated patients (n = 1241) has received a classical mediastinal field, including a relatively large part of the coronary arteries and the heart muscle. In addition, most patients were treated with one field per day only. The procedure of using 2 fields per day was gradually introduced in the late 1980s. Patients usually received 40 Gy in fractions of 2.0 Gy when they were treated with RT only and 30 to 36 Gy in fractions of (1.5-)2.0 Gy when they also received chemotherapy. Detailed information on radiation doses and fractionation schedules for individual patients was not collected.

From the 1960s to the 1980s chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were introduced as a part of the primary treatment (Table 1).

Table 1. Patient characteristics

Patient characteristics	HL patients, no. (%)
All patients	1474 (100)
Sex	
Male	790 (53.6)
Female	684 (46.4)
Age at start of treatment	
No older than 20 y[a]	314 (21.3)
21-25 y	363 (24.6)
26-30 y	296 (20.1)
31-35 y	266 (18.0)
Older than 35 y	235 (15.9)
Attained age at end of follow-up	
No older than 35 y	244 (16.6)
36-40 y	214 (14.5)
41-45 y	221 (15.0)
46-50 y	247 (16.8)
51-55 y	252 (17.1)
Older than 55 years	296 (20.1)
Treatment period	
Before 1974	416 (28.2)
1974-1982	477 (32.4)
1983-1995	581 (39.4)
Treatment[b]	
RT only	406 (27.5)
CT only	71 (4.8)
RT + CT, anthracylines	435 (29.5)
RT + CT, no anthracylines	559 (37.9)
Unknown	3 (0.2)
Radiotherapy[c]	
RT mediastinum[d]	1241 (84.2)
RT PAO or inverted Y with spleen[e]	410 (27.8)
RT PAO or inverted Y without spleen[f]	280 (19.0)
Type of chemotherapy	
MOPP[g]	255 (23.9)
ABVD[g]	38 (3.6)
MOPP/ABV[g]	189 (17.7)
Other combined CT[h]	496 (46.6)
Unknown	87 (8.2)
Vital status at date of last contact	
Alive	1017 (69.0)
Dead	457 (31.0)
Follow-up interval	
6-10 y	197 (13.4)
11-15 y	322 (21.8)
16-20 y	292 (19.8)
21-25 y	268 (18.2)
26-30 y	200 (13.6)
More than 30 y	195 (13.2)

Table 1. Patient characteristics (continued)

Patient characteristics	HL patients, no. (%)
Risk factors[i]	
Smoking[j]	
Recent	253 (17.2)
Ever	675 (45.8)
Never	541 (36.7)
Unknown	258 (17.5)
Hypertension	
Yes	147 (10.0)
No	1292 (87.7)
Unknown	35 (2.4)
Diabetes mellitus	
Yes	73 (5.0)
No	1381 (93.7)
Unknown	20 (1.4)
Hypercholesterolemia	
Yes	126 (8.5)
No	1316 (89.3)
Unknown	32 (2.2)

HL indicates Hodgkin lymphoma; RT, radiotherapy; CT, chemotherapy; PAO, para-aortic lymph nodes; inverted Y, para-aortic and iliac lymph nodes; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; EBVP, epirubicine, bleomycin, vinblastine, prednisone.

[a]Patients (n = 111) were 16 years or younger at HL diagnosis.

[b]Included primary and salvage therapies. RT includes all radiotherapy fields, not only mediastinal radiotherapy.

[c]Describing the most frequently used radiation fields.

[d]1114 during primary treatment.

[e]Patients (n = 372) received RT to the mediastinum, para-aortic lymph nodes (or inverted Y), and spleen.

[f]Patients (n = 240) received RT to both the mediastinum and the para-aortic lymph nodes (or inverted Y) without RT to the spleen.

[g]No other cytostatic drugs.

[h]Among those combinations, including MOPP (n = 167), MOPP/ABV (n = 51), ABVD (n = 73), and EBVP (n = 43).

[i]Data from oncology records and general practitioners, not from screening on cardiovascular risk factors.

[j]No mutually exclusive categories.

Statistical analysis

The incidence of CVDs in the study population was compared with the Netherlands population, using age-, sex-, and calendar period–specific incidence rates for the period from 1972 through 2000 from the Continuous Morbidity Registration Nijmegen (CMRN) from several Dutch GP practices.[21] Comparison of recent incidence rates of coronary heart disease (CHD),

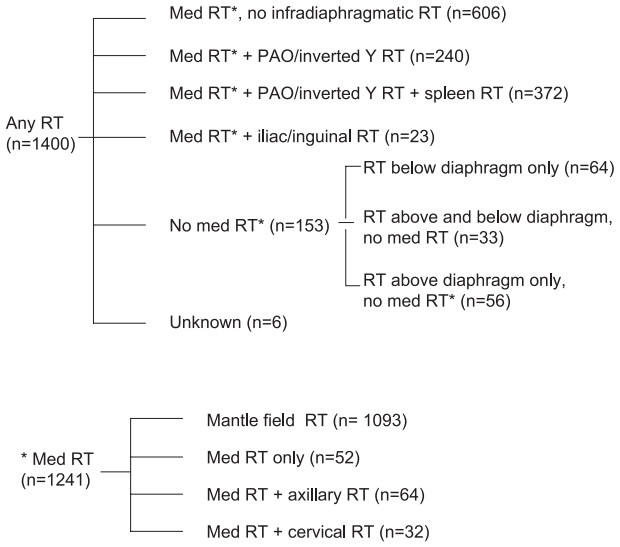

Figure 1. Flow chart of applied radiation fields. RT indicates radiotherapy; PAO, para-aortic; med, mediastinal; *Med RT, supradiaphragmatic radiotherapy including mediastinal radiotherapy; inverted Y, para-aortic and iliac nodes. Overall, 21% of the patients received radiotherapy including iliac nodes.

acute myocardial infarction (MI), and angina pectoris (AP) from the CMRN with incidence rates of several new registries in the Netherlands showed that incidence rates of the CMRN were similar to the mean of all registries combined, indicating that the CMRN is representative of the Netherlands.[22] Data on the incidence of MI, AP, and congestive heart failure (CHF) were registered by the CMRN, allowing for multiple separate diagnoses per person, but only the first of a given diagnosis was recorded.[23,24]

Because we included only 5-year survivors, time at risk started 5 years from HL diagnosis and ended at date of diagnosis of a specific cardiovascular event, date of emigration, date of death, or date of most recent medical information, whichever came first. When analyzing one specific cardiovascular diagnosis, observed numbers were based on all first events of this given diagnosis occurring at least 5 years after HL diagnosis, because the expected numbers of events were recorded correspondingly. Patients who were diagnosed with a specific cardiovascular event before HL diagnosis or within 5 years after HL diagnosis were excluded. In the analyses on CHD, comprising MI and AP, we excluded patients who were diagnosed with MI or AP before HL diagnosis or within 5 years after HL diagnosis. Two different approaches were used to assess risks for this combined diagnostic group. First, an analysis was performed in which both MI and AP were counted corresponding with the reference rates, which were also based on events rather than persons. Because different cardiovascular diagnoses may be more strongly correlated among our patients than in the general population, we also performed an analysis in which patients with both MI and AP contributed only one event to the observed numbers, with person-time at risk ending at the date of diagnosis of the first event, yielding conservative risk estimates.

For only 6.7% of patients, information on CVDs was not complete until at least July 1, 2002, date of death, or date of emigration. These patients contributed person-time and cardiovascular events until the date of most recent CVD information in the analyses. The standardized incidence ratios (SIRs) of the observed (O) and expected (E) numbers of MI, AP, CHF, and combined diagnostic groups in the study population were determined and the confidence intervals of the SIRs were calculated using exact Poisson probabilities of O numbers.[25] In addition, observed cumulative incidences of MI and AP in the study population were compared with expected cumulative incidences in their peers in the general population. *P* values for tests of heterogeneity and tests for trend were calculated according to standard methods.[26] Absolute excess risk (AER) was calculated as the observed number of CVDs in our cohort minus the number expected, divided by number of person-years at risk, multiplied by 10 000. The attributable risk (AR) was calculated as SIR minus 1 divided by SIR, multiplied by 100. Attained age was defined as the age of patients during follow-up and was calculated to assess at what ages patients experienced increased risk compared with their peers in the general population. Overall cardiovascular and diagnosis-specific risks were estimated using the Kaplan-Meier method.[27] Additionally, cumulative incidences of cardiovascular diseases were calculated with death from any cause as competing risk using S-plus statistical software (Insightful, Seattle, WA), including user-written functions.[28] Multivariable Cox regression analysis was performed to quantify the effects of different treatments on CVD risk within the patient group, adjusting for confounders. Cox models were fitted using SPSS statistical software (SPSS, Chicago, IL).

Results

General

Patient characteristics and distribution of risk factors for CVDs are described in Table 1. Twenty-eight percent of patients received RT only, 5% received CT alone, 38% received RT and CT not containing anthracyclines, and 29% received RT and CT including anthracyclines. Overall, 84% of patients received radiotherapy including the mediastinum. The median age at start of treatment was 25.7 years; median follow-up time was 18.7 years for the whole cohort (a total of 28 669 person-years) and 20.1 years for the 1017 patients alive at the end of follow-up. Thirty percent of the patients recently smoked cigarettes and 10% were diagnosed with hypertension.

Cardiovascular disease risk

We observed 619 CVDs at least 5 years from HL diagnosis in 354 of 1474 five-year survivors; 157 patients developed multiple CVDs (Table 2). Valvular disorders, AP and MI were the most common CVDs with 160, 134, and 102 events, respectively. The median time between start of treatment for HL and the diagnosis of CVDs was almost 19 years (Table 2).

The overall SIR for CHD was 4.0 (95% CI, 3.5-4.6) when all multiple events per patient were included (n = 233); and 3.2 (95% CI, 2.7-3.7) when only the first event was included (n = 182). SIRs were significantly elevated for MI (SIR = 3.6), AP (SIR = 4.1), and CHF (SIR = 4.9), resulting in 35.7 excess cases of MI, 49.6 excess cases of AP, and 25.6 excess cases of CHF per 10 000 person-years (Table 2). We observed significantly higher cumulative incidences of MI and AP in the study population compared with the general population (Figure 2).

The SIR for MI was significantly elevated beginning 10 years after treatment and remained increased with longer follow-up duration (Table 3). The AERs, however, increased with longer follow-up duration, because of the increasing incidence of CVD with age. After a follow-up of 25 years or more, 7 excess cases of MI were observed per 1000 person-years (Table 3). The SIRs of AP and CHF were more strongly elevated in patients treated for HL before the age of 20 years (Table 3). The decreasing trend of SIRs for CHF with older attained age was significant ($P < .001$).

There were no significant differences in SIRs of MI, AP, and CHF according to different treatment schedules (Table 3). The median follow-up after anthracycline-containing chemotherapy, however, was significantly lower (13.3 years) than after radiotherapy alone (22.2 years) or after radiotherapy in combination with chemotherapy not containing anthracyclines (21.9 years) (Table 1).

Table 2. Standardized incidence ratios of specific cardiac diseases in 5-year survivors of Hodgkin lymphoma

Diagnosis	ICD-9 codes	O	E	SIR	95% CI	AER*	Median interval, y (range)
Combined diagnostic group							
Coronary heart disease†	410, 413	233	57.7	4.0	3.5-4.6	87.0	20.2 (5.0-37.2)
Coronary heart disease‡	410, 413	182	57.7	3.2	2.7-3.7	61.7	20.2 (5.0-37.2)
Specific heart diseases							
Acute myocardial infarction	410	102§	28.5	3.6	2.9-4.4	35.7	19.5 (7.0-37.5)
Angina pectoris	413	134‖	32.4	4.1	3.5-4.9	49.6	20.7 (5.1-37.2)
Congestive heart failure	428	52¶	10.7	4.9	3.6-6.4	25.6	18.5 (5.0-39.0)
Pericarditis#	420, 423	23	—	—	—	—	13.6 (6.4-31.1)
Valvular disorders#	424	160	—	—	—	—	23.3 (5.0-37.8)
Cardiomyopathy#	425	33	—	—	—	—	18.0 (5.8-34.0)
Dysrhythmia#	427	89	—	—	—	—	18.3 (5.2-39.6)
All heart diseases#	410-429	619**	—	—	—	—	18.8 (5.0-39.6)

ICD-9 indicates International Classification of Diseases, 9th revision; CVD, cardiovascular disease; O, observed number of specific CVDs; E, expected number of specific CVDs; AER, absolute excess risk; —, not available; and NA, not applicable.

*Per 10 000 person-years. The absolute incidence rate/10 000 can be calculated with the following formula: AER + AER/(SIR − 1) × 10 000.

†Acute myocardial infarction and angina pectoris combined allowing both diagnoses per person; 51 patients had both diagnoses.

‡Acute myocardial infarction and angina pectoris combined allowing only 1 event per person.

§Includes 84 men and 18 women.

‖Includes 86 men and 48 women.

¶Congestive heart failure was observed in 59 patients but because reference rates are available from 1986, analyses were based on person-years and events since 1986; 7 patients with CHF before 1986 are excluded from this analysis.

#No reference rates available.

**In addition to the CVDs mentioned in the table: endocarditis (n = 6), cardiac aneurysm (n = 2) and sudden cardiac death (n = 11). Among patients with more than one CD frequently observed combinations were: CHF with valvular disorders (n = 29), CHF with AP (n = 22), CHF with MI (n = 14), CHF with cardiomyopathy (n = 10), dysrhythmia with MI (n = 14), dysrhythmia with AP (n = 31) and dysrhythmia with valvular disorders (n = 43). Among men in total, 356 cardiac events were observed consisting of MI (23.6%), AP (24.2%), valvular disorders (18.6%), dysrhythmia (12.9%), CHF (7.9%), cardiomyopathy (5.9%), pericarditis (3.4%), endocarditis (<1%), and cardiac aneurysm (<1%). Among women in total, 263 cardiac events were observed consisting of MI (6.8%), AP (18.3%), valvular disorders (35.7%), dysrhythmia (16.3%), CHF (11.8%), cardiomyopathy (4.6%), and pericarditis (4.2%).

Comparisons within the study cohort

In the multivariable Cox model analyses, treatment variables were adjusted for age at diagnosis, CVD risk factors, and recent smoking. Mediastinal radiotherapy significantly increased the risks of valvular disorders, CHD and CHF (Table 4). In addition, the risks of CHF and valvular disorders significantly increased when mediastinal radiotherapy was combined with anthracycline-containing chemotherapy (HR = 2.81; 95% CI = 1.44-5.49, and HR = 2.10; 95% CI = 1.27-3.48, respectively; Table 4, model 2). Established cardiovascular risk factors, except hypertension, increased the risk of most CVDs but did not appear to interact with treatment effects (Table 4, model 1).

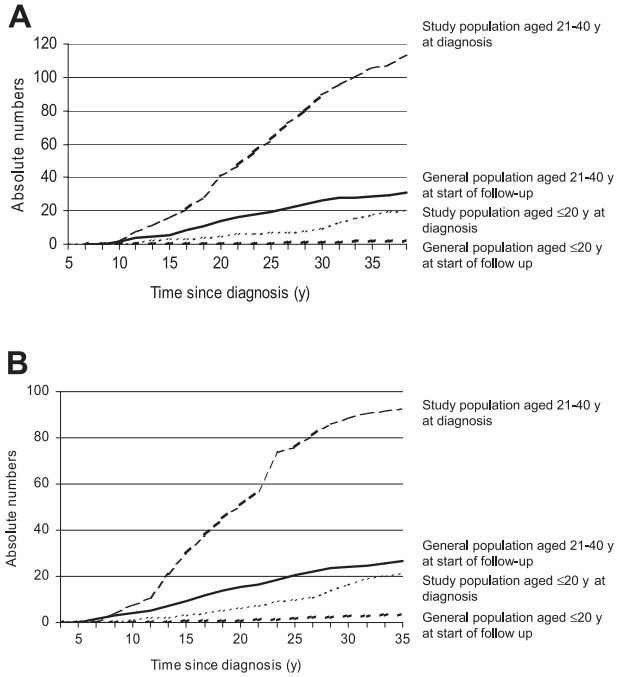

Figure 2. Observed and expected incidences of AP and MI by age among study population and peers from the general population. Observed and expected incidences of AP (A) and MI (B).

Of the 457 patients who died, the main causes of death were HL (n = 135), second primary malignancies (n = 137), and CVDs (n = 73; including 22 from MI). The overall 30-year cumulative incidence in mediastinally irradiated patients, using the competitive risk method, was 34.5% for any CVD, 12.9% for MI, and 19.7% for valvular disorders (Figure 3).

We compared actuarial risks of CHF or cardiomyopathy according to the Kaplan-Meier method with cumulative incidence with death from all causes as competing risk. The 25-year actuarial risks of CHF after mediastinal RT alone and mediastinal RT in combination with anthracycline-containing chemotherapy were 7.5% and 10.7%, respectively, whereas the cumulative incidences were lower (ie, 6.8% and 7.9%, respectively; Table 5).

Discussion

In our population of 5-year survivors of HL, we observed 3- to 5-fold increased incidences of several CVDs as compared with the general population, even after a follow-up of more than 25 years. This suggests that 66% to 80% of all CVDs in our population were due to HL treatment. CHD contributed most to the CVD burden, with 62 excess cases per 10 000 persons per year. The stably increased SIRs over prolonged follow-up are concerning because they imply increasing AERs over time, as a result of the rising incidence of CVD with age. The importance of assessing cardiovascular morbidity rather than mortality is illustrated by the fact that MI was nonfatal in 78% of our patient population.

Table 3. Risk of important cardiovascular diseases by sex, age at start of treatment, attained age, treatment, and follow-up interval

		Myocardial infarction				Angina pectoris				Congestive heart failure*			
	Person-y†	O	SIR	95% CI	AER‡	O	SIR	95% CI	AER‡	O	SIR	95% CI	AER‡
Sex													
Men	10 528	84	4.2	3.4-5.2	60.7	86	3.7	3.0-4.6	59.4	25	3.9	2.5-5.7	21.7
Women	10 034	18	2.1	1.2-3.3	9.4	48	5.2	3.8-6.9	39.1	27	6.4	4.2-9.4	29.8
Age at start of treatment													
No older than 20 y	4 892	9	5.4	2.4-10.3	15.0	20	11.6	7.0-17.9	37.2	11	18.2	9.0-32.6	27.6
21-25 y	5 227	25	5.9	3.8-8.7	39.7	30	6.2	4.2-8.8	48.1	11	7.0	3.5-12.5	23.1
26-30 y	4 111	22	4.1	2.6-6.2	40.4	30	4.8	3.2-6.9	58.6	13	6.7	3.6-11.5	34.7
31-35 y	3 746	24	2.7	1.8-4.1	40.7	26	2.6	1.7-3.9	43.5	8	2.5	1.1-4.9	16.0
36-40 y	2 630	22	2.6	1.6-4.0	51.8	28	2.9	1.9-4.2	70.2	9	2.7	1.2-5.1	26.4
Attained age§													
Younger than 40 y	10 353	13	4.4	2.3-7.5	9.7	17	6.0	3.5-9.6	13.7	9	26.0	11.8-49.5	12.6
40-49 y	6 974	44	4.0	2.9-5.4	47.4	51	3.8	2.8-5.0	53.8	19	5.1	3.1-8.1	25.8
At least 50 y	3 278	45	3.1	2.3-4.2	93.0	66	4.1	3.2-5.2	159.4	24	3.9	2.5-5.8	55.9
Treatment‖													
Initial RT only	6 551	36	3.9	2.7-5.4	49.9	54	5.2	3.9-6.7	66.8	18	4.8	2.8-7.6	27.1
RT + CT, no anthracyclines	8 994	50	3.9	2.9-5.1	66.0	57	3.8	2.9-5.0	47.0	25	5.3	3.4-7.8	31.8
RT + CT, anthracyclines	3 933	14	3.5	1.9-5.9	23.6	20	4.5	2.7-6.9	39.9	9	6.2	2.8-11.8	21.2
Initial CT only	1 083	2	1.0	0.1-3.5	7.4	2	0.8	0.1-2.9	−4.6	0	0.0	0.0-5.2	−8.2
Anthracycline-containing chemotherapy													
No	9 870	52	3.5	2.6-4.6	37.7	60	3.5	2.7-4.5	43.3	25	4.6	3.0-6.8	27.5
Yes	4 141	14	3.3	1.8-5.5	23.5	20	4.2	2.6-6.5	37.1	9	5.8	2.6-11.1	19.8
Follow-up interval													
5-9 y	6 872	7	1.7	0.7-3.6	4.3	12	2.6	1.3-4.5	10.7	5	7.1	2.3-16.8	11.0
10-14 y	5 457	24	4.4	2.8-6.5	33.9	21	3.3	2.0-5.1	26.8	5	3.4	1.1-7.9	8.7
15-19 y	3 861	24	4.0	2.5-5.9	46.4	25	3.5	2.2-5.1	46.0	19	8.5	5.1-13.2	47.3
20-24 y	2 443	26	4.7	3.1-7.0	84.0	30	4.6	3.1-6.5	96.7	6	2.4	0.9-5.2	13.7
At least 25 y	1 973	21	2.9	1.8-4.4	69.2	46	6.0	4.4-8.0	207.7	17	4.5	2.6-7.3	62.5

P values for trends were as follows: for myocardial infarction, $P = .001$ for age at start of treatment, $P = .17$ for attained age, and $P = .65$ for follow-up interval; for angina pectoris, $P < .001$ for age at start of treatment, $P = .43$ for attained age, and $P = .001$ for follow-up interval; and for congestive heart failure, $P < .001$ for age at start of treatment, $P < .001$ for attained age; and $P = .29$ for follow-up interval.

O indicates observed number of specific CVD; SIR, standardized incidence ratio; AER, absolute excess risk; RT, radiotherapy; CT, chemotherapy.

*Because reference rates are available from 1986, analyses were based on person-years and events since 1986. For this calculation the numbers of person-years for the follow-up periods from 20 years after diagnosis were similar as in the other analyses but differed for the follow-up periods until 19 years after diagnosis. The numbers of person-years for follow-up periods until 19 years were 5 to 9 years: 3907 person-years; 10 to 14 years: 4044 person-years; 15 to 19 years: 3541 person-years; 7 patients with CHF before 1986 are excluded from this analysis.

†Number of person-years for angina pectoris and congestive heart failure were similar to those for myocardial infarction.

‡Per 10 000 patients per year. The absolute incidence rate/10 000 can be calculated with the following formula: AER + AER/(SIR − 1) × 10 000.

§Attained age was defined as the age of patients at diagnosis of a given cardiovascular event or at the end of follow-up and was calculated to assess at what ages patients experienced increased risk compared with their peers in the general population. Each patient contributed person-years to each consecutive attained-age category that the patient passed through during follow-up.

‖RT includes all irradiated patients (n = 1400); see flow chart for detailed information. Three patients with incomplete treatment data were excluded from the analyses about treatment effects.

When evaluating specific treatment effects, we observed 2- to 7-fold increased risks of cardiotoxicity after irradiation, including part of the heart. Increased risks of death from radiation-associated CVD have been frequently described.[8-10,29-36] Radiation-induced CVD includes a wide spectrum of pathologies.[37,38] Damage of the vascular endothelium of arteries of different sizes is probably important in the explanation of radiation-induced heart disease.[37,39,40] The cause of valvular fibrosis, however, is yet unknown.

Radiation-induced cardiotoxicity is usually observed 5 to 10 years after radiotherapy. Now the standard therapy for most patients with HL includes anthracycline-containing chemotherapy. Anthracycline-related toxicity may be observed at different intervals after therapy. Despite the relatively short median observation time of 13 years after anthracycline-containing therapy, we observed a 2-fold increased risk of CHF and valvular disorders, on top of the effect of mediastinal radiotherapy.

The 25-year cumulative incidence of CHF and cardiomyopathy combined was 7.9% after mediastinal radiotherapy and anthracycline-containing chemotherapy. The risks of CVDs may further increase with prolonged follow-up. Anthracycline-associated cardiotoxicity is caused by direct damage to the myoepithelium and strongly related to the cumulative dose.[41,42] Although we did not record the cumulative dose of anthracyclines for individual patients, it is expected to be below 280 mg/m^2 because treatment for HL in both study centers usually consisted of maximally 8 cycles of MOPP/ABV. With the current shift to anthracycline-containing chemotherapy in HL, the doxorubicin dose will vary between 200 and 400 mg/m^2, possibly increasing the chemotherapy-related incidence of cardiotoxicity.

We observed higher SIRs of MI, AP, and CHF in patients treated at a young age, especially among those treated before age 20. In our publication on long-term mortality, largely concerning the same cohort as currently described, we demonstrated a 6-fold increased standardized mortality ratio from CVDs in patients with HL treated before age 41.[9] Other investigators also found age at irradiation to be a major determinant of mortality from CVD.[10,29,30] The higher risks in the patients treated at a younger age may partly be explained by low

Table 4. Multivariable Cox regression analysis of potential risk factors for cardiac diseases

Risk factor	MI	AP	CHF*	Valvular disorders
Model 1, no. of events	102	129	82	159
Treatment, HR (95% CI)†				
Mediastinal RT (yes vs no)	2.42 (1.12-5.24)	4.85 (1.97-11.9)	7.37 (1.81-30.0)	7.01 (2.59-18.9)
Anthracycline-containing CT (yes vs no)	0.90 (0.50-1.62)	1.49 (0.89-2.49)	2.44 (1.37-4.33)	2.24 (1.40-3.59)
Cardiovascular risk factors, HR (95% CI)				
Recent smoking (yes vs no/unknown)	2.04 (1.29-3.23)	1.35 (0.85-2.16)	1.96 (1.16-3.30)	1.23 (0.80-1.88)
Hypertension (yes vs no/unknown)‡	0.52 (0.29-0.94)	0.90 (0.58-1.42)	1.07 (0.59-1.94)	1.28 (0.86-1.92)
Hypercholesterolemia (yes vs no/unknown)‡	4.12 (2.68-6.33)	4.55 (3.10-6.68)	1.48 (0.85-2.58)	1.65 (1.11-2.44)
Diabetes mellitus (yes vs no/unknown)‡	1.44 (0.73-2.83)	2.43 (1.45-4.09)	4.45 (2.54-7.81)	1.81 (1.07-3.04)
Model 2, no. of events	95	124	80	155
Treatment group, HR (95% CI)§				
Mediastinal RT only‖	1.00	1.00	1.00	1.00
Mediastinal RT + CT, no anthracyclines¶	1.17 (0.75-1.83)	0.78 (0.53-1.15)	1.33 (0.79-2.24)	0.85 (0.60-1.21)
Mediastinal RT + CT, anthracyclines#	1.00 (0.52-1.94)	1.32 (0.76-2.30)	2.81 (1.44-5.49)	2.10 (1.27-3.48)

Forward stepwise confounder selection, in which the effect of adding one confounder at a time was evaluated, was based on a more than 10% change in the risk estimate of the exposure variable of interest, irrespective of significance values. Cardiovascular risk factors (hypertension, hypercholesterolemia, and diabetes mellitus) were included as confounders in the model, although they did not change the risk estimate for the treatment variables with more than 10%, because these are established confounders in the literature and informative as a comparison with the estimates for the treatment variables. All data were adjusted for recent smoking (yes versus no), age at diagnosis (continuous), and cardiovascular risk factors (hypertension, hypercholesterolemia, and diabetes mellitus). No interaction was found between RT and CT, or between treatment and recent smoking (investigated for RT and CT separately).

MI indicate myocardial infarction; AP, angina pectoris; CHF, congestive heart failure; HR, hazard ratio; RT, radiotherapy; CT, chemotherapy.

*Cardiomyopathy was included (n = 33, of whom 10 also had CHF).

†Includes primary and salvage treatment.

‡Patients were not screened for cardiovascular risk factors; data have been obtained from medical records and general practitioners.

§Patients who had not received mediastinal irradiation were excluded (n = 233).

‖Reference values.

¶Patients (n = 196) have been treated with the MOPP regimen only, 87 patients have been treated with the MOPP regimen and (an)other CT regimen(s).

#Patients (n = 153) have been treated with MOPP/ABV regimen only, 43 patients have been treated with the MOPP regimen and (an)other CT regimen(s), and 34 patients have been treated with the ABVD regimen only and 58 patients have been treated with the ABVD regimen and (an)other CT regimen(s).

background incidence rates of CVDs. Furthermore, immature cardiovascular tissue may be more vulnerable to radiation and chemotherapy.

Possibilities for primary and secondary prevention of chemotherapy-associated cardiotoxicity have been examined, using, for instance, altered infusion schedules and drugs such as iron chelators (dexrazoxane).[43] Dexrazoxane seems promising, but some investigators are concerned that it might diminish the efficacy of chemotherapy.[44]

The value of secondary prevention for CVDs is debatable. Subclinical cardiac damage has been shown in up to 57% of children or adults after treatment with anthracyclines and/or radiotherapy including part of the heart.[11,38,45,46] However, identification of patients at high risk to develop clinically important cardiotoxicity is not possible yet.[47,48] We showed that classical risk factors for cardiovascular diseases, except hypertension, increased the incidence of CVDs. Possibly hypertension did not increase CVD risk because patients with HL diagnosed with hypertension were adequately treated, whereas the reference group of patients without known hypertension may include undiagnosed hypertension. Patients with newly diagnosed HL and survivors of HL, especially when treated at young ages, should strongly be advised to refrain from smoking, to maintain a healthy body weight, and to exercise regularly. Furthermore, established risk factors for CVDs should be optimally treated in the patient population at increased risk of developing CVDs.[49] Screening may be considered, because the patient population at risk usually has a considerable life expectancy,[38,45] and these diagnostic procedures are noninvasive and relatively cheap. In the future, N-terminal pro–B-type natriuretic peptide (NT-proBNP) may also be used as a marker.[50,51] The role of prevention, using for instance anticoagulants, ACE-inhibitors, and statins, remains to be determined.

Our study has important strengths. To the best of our knowledge, we are the first to compare the incidences of several heart diseases in a large group of patients with HL treated with anthracycline-containing chemotherapy with the general population. A Swiss group compared the incidence of fatal and nonfatal cardiac disease in their study population (a relatively small group of mediastinally irradiated patients with HL treated with or without chemotherapy) with the incidence in the US Framingham population. A significantly increased risk of ischemic heart disease was observed only in patients with established cardiovascular disease risk factors.[14] Incidence rates of hospitalization for ischemic heart disease[35] and of utilization of valve surgery, percutaneous interventions, and coronary bypass graft surgery among patients with HL,[52] compared with general population rates, have been used as surrogate markers for CVD incidence. Furthermore, we achieved complete follow-up on both cardiac morbidity and mortality, whereas most studies assessed cardiac mortality only, thus underestimating the importance of CVD as a long-term complication of HL treatment. In addition, we calculated not only actuarial risks[27] but also cumulative incidences with death from any cause as competing risk.[28] The results show that the Kaplan-Meier actuarial risk method overestimates CVD risk, because it wrongly assumes that dead patients, had they lived longer, would have had the same CVD risk as surviving patients.[28] Potential weaknesses of our study are the relatively short follow-up after anthracycline-containing chemotherapy, the lack of the possibility to study the effects of (anthracycline-containing) chemotherapy only, and the lack of more detailed information on chemotherapy and radiation doses.

During the study period, treatment strategies and prognosis for patients with HL have changed tremendously.[20] In the current study, 84% of the patients received mediastinal radiation, whereas in the future only a minority of patients will need this. Approximately two thirds of patients with HL present with mediastinal localizations, but not all of them will need to be irradiated, and, if so, the target volume will be much more limited than before. Decline of the increased risk of death from

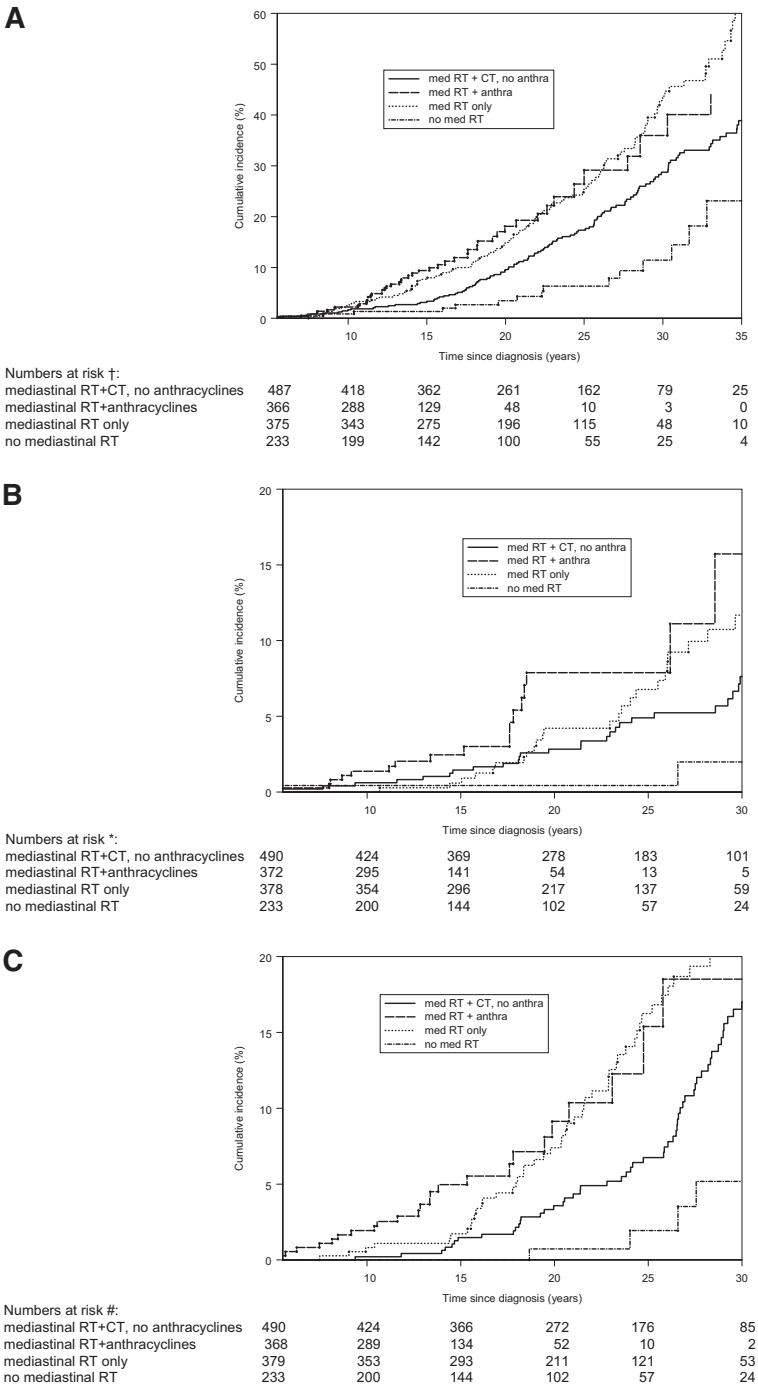

Figure 3. Cumulative incidences of various CVDs by treatment group, with death from any cause other than CVD as competing risk. (A) Cumulative incidence of all CVDs combined by treatment group with death from any cause as competing risk. Med RT indicates mediastinal RT; CT, chemotherapy; anthra, anthracyclines; MI, myocardial infarction; AP, angina pectoris; and CHF, congestive heart failure. †Thirteen patients were excluded from this analysis because they developed MI, AP, or CHF before or within 5 years after HL diagnosis. (B) Cumulative incidence of CHF and cardiomyopathy combined by treatment group with death from any cause as competing risk. Med RT, mediastinal RT; CT, chemotherapy; anthra, anthracyclines; CHF, congestive heart failure. *One patient was excluded from this analysis because CHF developed before or within 5 years after HL diagnosis. (C) Cumulative incidence of valvular disorders by treatment group, with death from any cause as competing risk. Med RT indicates mediastinal RT; CT, chemotherapy; anthra, anthracyclines. #Four patients were excluded from this analysis because they developed valvular disorders before or within 5 years after HL diagnosis.

CVDs other than MI has already been reported after partial shielding of the heart and a reduction of the total radiation dose to the mediastinum below 30 Gy.[10] In addition, radiotherapy techniques have greatly improved, leading to more homogeneous dose distributions and therefore to a lower chance of toxicity.[53] Partial shielding of the heart[10] was applied in our cohort, depending on tumor localization. We could not examine possible dose-effect or dose-volume relations because details on radiation dose and volume were not collected.

In summary, patients with HL experience a strongly increased risk of various CVDs for a prolonged period after treatment. Mediastinal radiotherapy and anthracycline-containing chemotherapy importantly contribute to cardiac late effects. Especially in young survivors of HL at increased risk of CVD, physicians should consider appropriate risk-reducing strategies such as treatment of hypertension and hypercholesterolemia, and lifestyle advice such as refraining from smoking.

Acknowledgments

We thank S. Grivell, J. Huisbrink, and L. D. Dorresteijn for collecting data. We thank E. H. van de Lisdonk from CMR-Nijmegen for supplying us with incidence rates. We are indebted to thousands of physicians from throughout the Netherlands who provided follow-up data for the study.

This work was supported by the Dutch Cancer Society, Amsterdam, The Netherlands (grants NKI 98-1833 and NKI 04-3068).

Table 5. Actuarial risk of CHF and cardiomyopathy combined in 5-year survivors of HL according to the Kaplan-Meier method versus cumulative incidence with death from any cause as competing risk

Treatment group	Time since diagnosis†					
	10 y, %	15 y, %	20 y, %	25 y, %	30 y, %	35 y, %
Actuarial risk according to the Kaplan-Meier method*						
No mediastinal RT	0.4	0.4	0.4	0.4	2.5	2.5
Mediastinal RT only	0.0	0.6	4.5	7.5	13.9	13.9
Mediastinal RT + CT, no anthracyclines	0.7	1.7	3.5	6.5	11.3	24.8
Mediastinal RT + anthracyclines	1.5	2.8	10.7	10.7	29.8	NA
All treatments	0.7	1.5	4.4	6.7	12.2	20.0
Cumulative incidence with death from any cause as competing risk*						
No mediastinal RT	0.4	0.4	0.4	0.4	2.0	2.0
Mediastinal RT only	0.0	0.6	4.2	6.8	11.7	11.7
Mediastinal RT + CT, no anthracyclines	0.6	1.5	2.8	4.9	7.6	14.3
Mediastinal RT + anthracyclines	1.4	2.5	7.9	7.9	15.7	NA
All treatments	0.6	1.3	3.7	5.4	8.9	13.1

CHF indicates congestive heart failure; RT, radiotherapy; CT, chemotherapy; NA, not applicable because there were no patients at risk in this subgroup.

*The median age at diagnosis was similar for the different treatment groups.

†Because only patients who survived at least 5 years after HL diagnosis and patients without previous CVDs are included, the cumulative incidence at 5 years is 0% for all patients.

Authorship

Contribution: B.M.P.A., A.W.v.d.B.-D., and F.E.v.L. contributed to the design of the study. B.M.P.A., A.W.v.d.B.-D., M.L.D.B., A.A.M.H., W.J.K., and F.E.v.L. were involved with the data analysis and interpretation. M.A.K. and G.M.O. contributed to collection of data and administrative support. B.M.P.A., A.W.v.d.B.-D., M.L.D.B., M.B.v.V., M.H.A.B., J.P.d.B., A.A.M.H., W.J.K., H.B., and F.E.v.L. contributed to the writing of the report. All authors approved the final manuscript.

Conflict of interest disclosure: The authors declare no competing financial interests.

B.M.P.A. and A.W.v.d.B.-D. contributed equally to the study.

Correspondence: Flora E. van Leeuwen, Department of Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; e-mail: F.v.Leeuwen@nki.nl.

References

1. Diehl V, Thomas RK, Re D. Part II: Hodgkin's lymphoma—diagnosis and treatment. Lancet Oncol. 2004;5:19-26.
2. Hancock SL, Hoppe RT. Long-term complications of treatment and causes of mortality after Hodgkin's disease. Semin Radiat Oncol. 1996;6: 225-242.
3. Lee CK, Aeppli D, Nierengarten ME. The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. Int J Radiat Oncol Biol Phys. 2000;48:169-179.
4. Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol. 2000;18:2435-2443.
5. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000;18:498-509.
6. van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol. 2000;18:487-497.
7. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. 2002;20:3484-3494.
8. Ng AK, Bernardo MP, Weller E, et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol. 2002;20: 2101-2108.
9. Aleman BM, Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003; 21:3431-3439.
10. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA. 1993;270: 1949-1955.
11. Kremer LC, van der Pal HJ, Offringa M, van Dalen EC, Voute PA. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol. 2002;13:819-829.
12. Yeh ET, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation. 2004;109:3122-3131.
13. Brierley JD, Rathmell AJ, Gospodarowicz MK, et al. Late effects of treatment for early-stage Hodgkin's disease. Br J Cancer. 1998;77:1300-1310.
14. Glanzmann C, Kaufmann P, Jenni R, Hess OM, Huguenin P. Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol. 1998;46:51-62.
15. King V, Constine LS, Clark D, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1996;36:881-889.
16. van Spronsen DJ, Post PN, Crommelin MA, Breed WP, Coebergh JW. Modest decline in late mortality following Hodgkin's disease in the southeastern Netherlands since 1972. Ann Hematol. 1998;76:205-209.
17. Aviles A, Neri N, Nambo JM, et al. Late cardiac toxicity secondary to treatment in Hodgkin's disease: a study comparing doxorubicin, epirubicin and mitoxantrone in combined therapy. Leuk Lymphoma. 2005;46:1023-1028.
18. Koontz BF, Kirkpatrick JP, Clough RW, et al. Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. J Clin Oncol. 2006;24:605-611.
19. van Leeuwen FE, Klokman WJ, Hagenbeek A, et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol. 1994;12:312-325.
20. Eghbali H, Raemaekers J, Carde P. The EORTC strategy in the treatment of Hodgkin's lymphoma. Eur J Haematol Suppl. 2005;135-140.
21. van den Belt-Dusebout AW, Nuver J, de Wit R, et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol. 2006;24:467-475.
22. Gijsen R, Poos MJJM. Coronaire hartziekten: omvang van het probleem: achtergronden en details bij cijfers uit huisartsenregistraties. Rijksinstituut voor Volksgezondheid en Milieu. http://www.rivm.nl/vtv/object_document/o3171n17964.html. Accessed on February 15, 2005.
23. van de Lisdonk EH, van den Bosch WJHM, Huygen FJA, Lagro-Jansen ALM. Ziekten in de huisartspraktijk. 3rd ed. Maarssen, The Netherlands: Elsevier/Bunge; 1999.
24. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978-1994. Eur Heart J. 1998;19:429-434.
25. Pearson ES, Hartley HO, eds. Biometrika tables for statisticians. London, United Kingdom: Biometrika Trust; 1976.
26. Breslow NE, Day NE. Statistical Methods in Cancer Research. Vol 2. The Design and Analysis of

Cohort Studies. Lyon, France: IARC Scientific Publications; 1987.

27. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-481.
28. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18:695-706.
29. Henry-Amar M, Hayat M, Meerwaldt JH, et al. Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. EORTC Lymphoma Cooperative Group. Int J Radiat Oncol Biol Phys. 1990;19:1155-1157.
30. Cosset JM, Henry-Amar M, Meerwaldt JH. Long-term toxicity of early stages of Hodgkin's disease therapy: the EORTC experience. EORTC Lymphoma Cooperative Group. Ann Oncol. 1991; 2(suppl 2):77-82.
31. Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer. 1992;69: 1241-1247.
32. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol. 1993; 11:1208-1215.
33. Mauch PM, Kalish LA, Marcus KC, et al. Long-term survival in Hodgkin's disease. Cancer J Sci Am. 1995;1:33-42.
34. Hoppe RT. Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol. 1997; 8(suppl 1):115-118.
35. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, van Putten WL, Levendag PC. Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radiother Oncol. 1999;51:35-42.
36. Aviles A, Neri N, Cuadra I, Alvarado I, Cleto S. Second lethal events associated with treatment for Hodgkin's disease: a review of 2980 patients treated in a single Mexican institute. Leuk Lymphoma. 2000;39:311-319.
37. Adams MJ, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. Pediatr Blood Cancer. 2005;44:600-606.
38. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003;42:743-749.
39. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol. 1996;27:766-773.
40. Stewart FA, Heeneman S, Te PJ, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. Am J Pathol. 2006;168:649-658.
41. Steinherz LJ. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1997;126:827-828.
42. Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. J Clin Oncol. 2001;19:191-196.
43. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004;351:145-153.
44. van Dalen EC, van der Pal HJ, van den BC, Caron HN, Kremer LC. Treatment for asymptomatic anthracycline-induced cardiac dysfunction in childhood cancer survivors: the need for evidence. J Clin Oncol. 2003;21:3377-3378.
45. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol. 2004;22:3139-3148.
46. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol. 2004;22:1864-1871.
47. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. Heart. 2004;90:1214-1216.
48. Girinsky T, Cordova A, Rey A, et al. Thallium-201 scintigraphy is not predictive of late cardiac complications in patients with Hodgkin's disease treated with mediastinal radiation. Int J Radiat Oncol Biol Phys. 2000;48:1503-1506.
49. Mauch P, Ng A, Aleman B, et al. Report from the Rockefellar Foundation Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. Eur J Haematol Suppl. 2005;68-76.
50. Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem. 2005;51:1405-1410.
51. Richards M, Nicholls MG, Espiner EA, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. J Am Coll Cardiol. 2006; 47:52-60.
52. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA. 2003;290:2831-2837.
53. Lee SP, Leu MY, Smathers JB, et al. Biologically effective dose distribution based on the linear quadratic model and its clinical relevance. Int J Radiat Oncol Biol Phys. 1995;33:375-389.