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 Leeuwen2

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

© 2007 by The American Society of Hematology
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.

Radiotherapy was introduced as a part of the primary treatment (Table 1).

From the 1960s to the 1980s chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone), ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine; EBVP, epirubicin, bleomycin, vinblastine, prednisone.

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

**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),
Standard methods. Absolute excess risk (AER) was calculated as the cumulative incidences in their peers in the general population. The probabilities of occurrence were approximated using Poisson statistics. In the analyses of CHF, 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 included, and in the second, only one event was included, yielding the AERs, which were calculated with death from any cause as competing risk.

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 containing 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 1,017 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 1,474 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 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 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 ($P < 0.001$).

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).
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).

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.
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/m² 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/m², 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 3. Risk of important cardiovascular diseases by sex, age at start of treatment, attained age, treatment, and follow-up interval**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Myocardial infarction</th>
<th>Angina pectoris</th>
<th>Congestive heart failure*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-y†</td>
<td>O SIR 95% CI</td>
<td>AER‡</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10 528</td>
<td>84 4.2 3.4-5.2</td>
<td>60.7 86 3.7 3.0-4.6 59.4 25 3.9 2.5-5.7 21.7</td>
</tr>
<tr>
<td>Women</td>
<td>10 034</td>
<td>18 2.1 1.2-3.3</td>
<td>9.4 48 5.2 3.9-6.9 39.1 27 6.4 4.2-9.4 29.8</td>
</tr>
<tr>
<td><strong>Age at start of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No older than 20 y</td>
<td>4 892</td>
<td>9 5.4 2.4-10.3</td>
<td>15.0 20 11.6 7.0-17.9 37.2 11 18.2 9.0-32.6 27.6</td>
</tr>
<tr>
<td>21-25 y</td>
<td>5 227</td>
<td>25 5.9 3.8-8.7</td>
<td>39.7 30 6.2 4.2-8.8 48.1 11 7.0 3.5-12.5 23.1</td>
</tr>
<tr>
<td>26-30 y</td>
<td>4 111</td>
<td>22 4.1 2.6-6.2</td>
<td>40.4 30 4.8 3.2-6.9 58.6 13 6.7 3.6-11.5 34.7</td>
</tr>
<tr>
<td>31-35 y</td>
<td>3 746</td>
<td>24 2.7 1.8-4.1</td>
<td>40.7 26 2.6 1.7-3.9 43.5 8 2.5 1.1-4.9 16.0</td>
</tr>
<tr>
<td>36-40 y</td>
<td>2 630</td>
<td>22 2.6 1.6-4.0</td>
<td>51.8 28 2.9 1.9-4.2 70.2 9 2.7 1.2-5.1 26.4</td>
</tr>
<tr>
<td><strong>Atained age§</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 40 y</td>
<td>10 353</td>
<td>13 4.4 2.3-7.5</td>
<td>9.7 17 6.0 3.5-9.6 13.7 9 26.0 11.8-49.5 12.6</td>
</tr>
<tr>
<td>40-49 y</td>
<td>6 974</td>
<td>44 4.0 2.9-5.4</td>
<td>47.4 51 3.8 2.8-5.0 53.8 19 5.1 3.1-8.1 25.8</td>
</tr>
<tr>
<td>At least 50 y</td>
<td>3 278</td>
<td>45 3.1 2.3-4.2</td>
<td>93.0 66 4.1 3.2-5.2 159.4 24 3.9 2.5-5.8 55.9</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial RT only</td>
<td>6 551</td>
<td>36 3.9 2.7-5.4</td>
<td>49.9 54 5.2 3.9-6.7 66.8 18 4.8 2.8-7.6 27.1</td>
</tr>
<tr>
<td>RT + CT, no anthracyclines</td>
<td>8 994</td>
<td>50 3.9 2.9-5.1</td>
<td>66.0 57 3.8 2.9-5.0 47.0 25 5.3 3.4-7.8 31.8</td>
</tr>
<tr>
<td>RT + CT, anthracyclines</td>
<td>3 933</td>
<td>14 3.5 1.9-5.9</td>
<td>23.6 20 4.5 2.7-5.9 39.9 9 6.2 2.8-11.8 21.2</td>
</tr>
<tr>
<td>Initial CT only</td>
<td>1 083</td>
<td>2 1.0 0.1-3.5</td>
<td>7.4 2 0.8 0.1-2.9 4.6 0 0.0 0.0-5.2 -8.2</td>
</tr>
<tr>
<td><strong>Anthracycline-containing chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 870</td>
<td>52 3.5 2.6-4.6</td>
<td>37.7 60 3.5 2.7-4.5 43.3 25 4.6 3.0-6.8 27.5</td>
</tr>
<tr>
<td>Yes</td>
<td>4 141</td>
<td>14 3.3 1.8-5.5</td>
<td>23.5 20 4.2 2.6-5.5 37.1 9 5.8 2.6-11.1 19.8</td>
</tr>
<tr>
<td><strong>Follow-up interval</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9 y</td>
<td>6 672</td>
<td>7 1.7 0.7-3.6</td>
<td>4.3 12 2.6 1.3-4.5 10.7 5 7.1 2.3-16.8 11.0</td>
</tr>
<tr>
<td>10-14 y</td>
<td>5 457</td>
<td>24 4.4 2.8-6.5</td>
<td>33.9 21 3.3 2.0-5.1 26.8 5 3.4 1.1-7.9 8.7</td>
</tr>
<tr>
<td>15-19 y</td>
<td>3 861</td>
<td>24 4.0 2.5-5.9</td>
<td>46.4 25 3.5 2.2-5.1 46.0 19 8.5 5.1-13.2 47.3</td>
</tr>
<tr>
<td>20-24 y</td>
<td>2 443</td>
<td>26 4.7 3.7-7.0</td>
<td>84.0 30 4.6 3.1-6.5 96.7 6 2.4 0.9-5.2 13.7</td>
</tr>
<tr>
<td>At least 25 y</td>
<td>1 973</td>
<td>21 2.9 1.8-4.4</td>
<td>69.2 46 6.0 4.4-8.0 207.7 17 4.5 2.6-7.3 62.5</td>
</tr>
</tbody>
</table>

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 angina pectoris and congestive heart failure were similar to those for myocardial infarction.

†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 = SIR × (1 - O/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.
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).45 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 disease15 and utilization of valve surgery, percutaneous interventions, and coronary bypass graft surgery among patients with HL,32 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 risks27 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.26 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
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. In addition, radiotherapy techniques have greatly improved, leading to more homogeneous dose distributions and therefore to a lower chance of toxicity. Partial shielding of the heart 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. Huishrink, 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

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>10 y, %</th>
<th>15 y, %</th>
<th>20 y, %</th>
<th>25 y, %</th>
<th>30 y, %</th>
<th>35 y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mediastinal RT</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Mediastinal RT only</td>
<td>0.0</td>
<td>0.6</td>
<td>4.5</td>
<td>7.5</td>
<td>13.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Mediastinal RT + CT, no anthracyclines</td>
<td>0.7</td>
<td>1.7</td>
<td>3.5</td>
<td>6.5</td>
<td>11.3</td>
<td>24.8</td>
</tr>
<tr>
<td>Mediastinal RT + anthracyclines</td>
<td>1.5</td>
<td>2.8</td>
<td>10.7</td>
<td>10.7</td>
<td>29.8</td>
<td>NA</td>
</tr>
<tr>
<td>All treatments</td>
<td>0.7</td>
<td>1.5</td>
<td>4.4</td>
<td>6.7</td>
<td>12.2</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Cumulative incidence with death from any cause as competing risk*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>10 y, %</th>
<th>15 y, %</th>
<th>20 y, %</th>
<th>25 y, %</th>
<th>30 y, %</th>
<th>35 y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mediastinal RT</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Mediastinal RT only</td>
<td>0.0</td>
<td>0.6</td>
<td>4.2</td>
<td>6.8</td>
<td>11.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Mediastinal RT + CT, no anthracyclines</td>
<td>0.6</td>
<td>1.5</td>
<td>2.8</td>
<td>4.9</td>
<td>7.6</td>
<td>14.3</td>
</tr>
<tr>
<td>Mediastinal RT + anthracyclines</td>
<td>1.4</td>
<td>2.5</td>
<td>7.9</td>
<td>7.9</td>
<td>15.7</td>
<td>NA</td>
</tr>
<tr>
<td>All treatments</td>
<td>0.6</td>
<td>1.3</td>
<td>3.7</td>
<td>5.4</td>
<td>8.9</td>
<td>13.1</td>
</tr>
</tbody>
</table>

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


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


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


Late cardiotoxicity after treatment for Hodgkin lymphoma

Berthe M. P. Aleman, Alexandra W. van den Belt-Dusebout, Marie L. De Bruin, Mars B. van ‘t Veer, Margreet H. A. Baaijens, Jan Paul de Boer, Augustinus A. M. Hart, Willem J. Klokman, Marianne A. Kuenen, Gabey M. Ouwens, Harry Bartelink and Flora E. van Leeuwen

Updated information and services can be found at:
http://www.bloodjournal.org/content/109/5/1878.full.html

Articles on similar topics can be found in the following Blood collections
- Clinical Trials and Observations (4542 articles)
- Neoplasia (4182 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml