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Chapter 7

Valvular abnormalities detected by echocardiography in 5-year survivors of childhood cancer: a long-term follow-up study

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Summary

Childhood cancer survivors who received cardiotoxic therapy are at risk for heart disease. We report the prevalence of echocardiographically detected valvular abnormalities in long-term survivors treated with radiotherapy to the heart region and/or anthracyclines. We observed one or more, mainly mild, valvular abnormalities in almost one third of the survivors. Multivariable regression analyses showed that, besides the presence of congenital heart disease, higher radiotherapy dose was the most important risk factor.

Abstract

Purpose

To determine the prevalence of valvular abnormalities after radiotherapy involving the heart region and/or treatment with anthracyclines and to identify associated risk factors in a large cohort of 5-year childhood cancer survivors (CCS).

Methods and Materials

The study cohort consisted of all 626 eligible 5-year CCS diagnosed with childhood cancer in the Emma Children's Hospital/Academic Medical Center between 1966 and 1996 and treated with radiotherapy involving the heart region and/or anthracyclines. We determined the presence of valvular abnormalities based on echocardiograms. Physical radiation dose was converted into the equivalent dose in 2-Gy fractions (EQD_2). Using multivariable logistic regression analyses, we examined the associations between cancer treatment and valvular abnormalities.

Results

We identified 225 mainly mild echocardiographic valvular abnormalities in 169 of 545 CCS (31%) with a cardiac assessment (median follow-up time of 14.9 years (range 5.1-36.8), median attained age of 22.0 years (range 7.0-49.7)). Most common abnormalities were tricuspid valve disorders (N=119; 21.8%) and mitral valve disorders (N=73; 13.4%). The risk of valvular abnormalities was associated with increasing radiotherapy dose to the heart region, expressed as EQD_2 (OR 1.33 per 10 Gray) and the presence of congenital heart disease (OR 3.43).

Conclusion

Almost one third of CCS treated with potentially cardiotoxic therapy had one or more mostly mild valvular abnormalities after a median follow-up of nearly 15 years. The most important risk factors are higher irradiation dose expressed as EQD_2 and congenital heart disease.

Introduction

Effective treatment strategies have greatly improved childhood cancer survival. With 5-year overall survival approaching 80%, most children diagnosed with cancer today will become long-term survivors.[1] However, improved prognosis has been accompanied by long-term health problems due to cancer treatment. Approximately 75% of survivors experience one or more adverse events.[2,3] Cardiovascular disease and mortality are among the most serious late effects.[4-8] Several studies observed a 6- to 8-fold increased mortality due to CVD among childhood cancer survivors (CCS) compared to the general population.[9-13] Cardiac disease and mortality are predominantly associated with treatment with radiotherapy involving the heart region and/or anthracyclines.[4-27]

Radiotherapy involving the heart region can adversely affect the heart structures, including the pericardium, myocardium, valves, conduction system and coronary arteries. This may lead to cardiac diseases such as valvular disease, congestive heart failure and coronary artery disease.[14,26] Several risk factors, like higher radiation dose, younger age at exposure, larger volume of heart exposed, and radiation technique have been identified, but not consistently in all studies.[14,26]

In a previous study, we showed that after 30 years one in eight CCS treated with both radiotherapy to the heart region and anthracyclines will develop severe heart disease. The risk of developing symptomatic valvular disease, defined as severe or life-threatening or disabling valvular disease requiring treatment, was predominantly associated with radiotherapy involving the heart region; the 30-year cause-specific cumulative incidence was 2.5% for CCS treated with radiotherapy to the heart region compared to 0.1% for other treatments.[7]

Only a few studies have evaluated both symptomatic and asymptomatic valvular disease after treatment for childhood cancer.[5,7,15,19] The outcome of these studies varied regarding incidence, type and hemodynamic significance of the identified valvular lesions. The prevalence of asymptomatic and symptomatic valvular disease after childhood cancer treatment is largely unknown; reported frequencies vary from 1.6% to over 40% with different definitions, diagnostic methods, and study groups.[5,7,15,26] The precise role of anthracyclines and other chemotherapeutic agents, in relation to the risk of valvular disease has to be determined.[5,11,28]

The aim of our study was to determine the prevalence of valvular abnormalities measured by echocardiography after radiotherapy involving the heart region and/or treatment with anthracyclines, and to identify associated risk factors in a large cohort of 5-year CCS. This knowledge can contribute to optimal recommendations for less toxic treatments, to preventive measures during or after treatment and to optimal follow-up care for survivors.

Methods and materials

Study population

The study population was selected from a cohort of all children (<18 years) diagnosed with childhood cancer in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC), Amsterdam, the Netherlands, between January 1st 1966 and January 1st 1996, and who survived for ≥5 years after diagnosis. Patient selection and data collection have been described previously.[2,29] Patients were identified using the Childhood Cancer Registry of the EKZ/AMC. This registry, established in 1966, contains data on all patients treated for childhood cancer in the EKZ/AMC regarding diagnosis, treatment, and follow-up. To be eligible for inclusion in this study, patients had to meet the following criteria: 1) diagnosis of a primary malignancy between 1966 and 1996, 2) age <18 years at time of primary diagnosis, 3) ≥5 year survival after diagnosis, 4) treated primarily in EKZ/AMC, 5) treated with radiotherapy involving the heart region and/or anthracyclines.

Data collection and follow-up

In 1996, the Outpatient Clinic for Late Effects of Childhood Cancer was established in the EKZ/AMC, after approval by the hospital's Institutional Review Board. All 5-year CCS were traced using the Childhood Cancer Registry and invited to participate in prospective follow-up protocols tailored to previous diagnosis and treatment. The CCS gave informed consent for data collection from the medical records[2]. CCS who received treatment with radiotherapy involving the heart region and/or treatment with anthracyclines were enrolled in the cardiotoxicity screening protocol that comprised a full medical assessment including an echocardiography on the same day.

We extracted information concerning patient characteristics, cancer diagnoses, therapy including treatment for recurrence(s), date of last medical follow-up and presence of valvular abnormalities directly from the Childhood Cancer Registry or from medical records. For each patient, we recorded: cumulative dose of all chemotherapeutic agents, radiotherapy dose, date and cause of death (if applicable), and presence of congenital heart disease, defined as a clinically relevant defect in the structure of the heart or great vessels considered present at birth. We defined potentially cardiotoxic therapy as treatment with radiotherapy involving the heart region and/or anthracyclines for a first childhood malignancy and/or recurrent disease with or without other treatments. Radiotherapy involving the heart region was defined as thoracic, spinal, abdominal (including upper, left or whole abdomen, para-aortic lymph nodes or inverted Y) irradiation and TBI.

The physical radiation dose was converted into the equivalent dose in 2-Gray fractions (EQD_2).[7,30] which enabled us to uniformly compare the diverse fractionation schedules used over time. The EQD_2 however, does not correspond to the exact dose received by the valves; it is the applied dose to the heart region. More information on EQD_2 is presented in the Appendix.

Cardiac assessment

For each patient, the first evaluable echocardiogram performed at least 5 years after diagnosis was used as outcome measurement. Measurements were made by trained echocardiography technicians and approved and interpreted by experienced cardiologists from our hospital who were blinded to the specific details of therapy. We defined a valvular abnormality as a grade mild or higher functional defect in the mitral, aortic, tricuspid and/or pulmonary valve identified with echocardiographic assessment. We considered trace abnormalities as physiological conditions with no clinically relevant consequences. Valvular function assessment is described in detail in the Appendix. [31-34]

Statistical analyses

In this cross-sectional study, we determined both the prevalence of a single valvular abnormality and the prevalence of mitral, tricuspid, pulmonary and aortic valve abnormalities combined. Physiological valvular abnormalities were considered normal and analyzed as such. To investigate potential risk factors for the valvular abnormalities, multivariable logistic regression analyses were performed for any echocardiographic valvular abnormality, and for tricuspid and mitral valve abnormalities separately. For aortic and pulmonary valve abnormalities we only present descriptive results, due to the low numbers of abnormal findings. We included the following potential determinants of valvular abnormalities in our models: sex, age at cancer diagnosis, cumulative dose of anthracyclines, cyclophosphamide, ifosfamide, cisplatin, and vincristine, cardiac irradiation dose (EQD_2), irradiation fields and congenital heart disease. In the first model, we quantified the effect of cumulative cardiac irradiation dose and in the second model we evaluated the effect of cardiac irradiation dose per radiation field (both expressed as the odds ratio (OR) per 10 Gy EQD_2). It should be noted that the ORs resulting from the analyses cannot be interpreted as relative risks because of the high (>10%) overall prevalence of valvular abnormalities. All analyses were corrected for follow-up time, i.e. the time between date of primary cancer diagnosis and date of cardiac assessment. Finally, we investigated a possible interaction between congenital heart disease and cardiac irradiation dose. Analyses were performed using statistical software SPSS for Windows version 20.0 (SPSS, Inc, Chicago, IL).

Results

Study population

Between January 1966 and January 1996, 2596 patients were diagnosed with childhood cancer in the EKZ/AMC. Of those, 1362 survived for ≥5 years (Figure 1). In total, 723 patients were treated with potentially cardiotoxic therapy. Ninety-seven 5-year CCS died before they could visit our outpatient clinic; none due to valvular abnormalities. Thus, 626 CCS were eligible for inclusion; 545 had an evaluable echocardiogram (87.1%). Echocardiograms of eight survivors were not evaluable due to poor quality. The other 73 patients did not have an

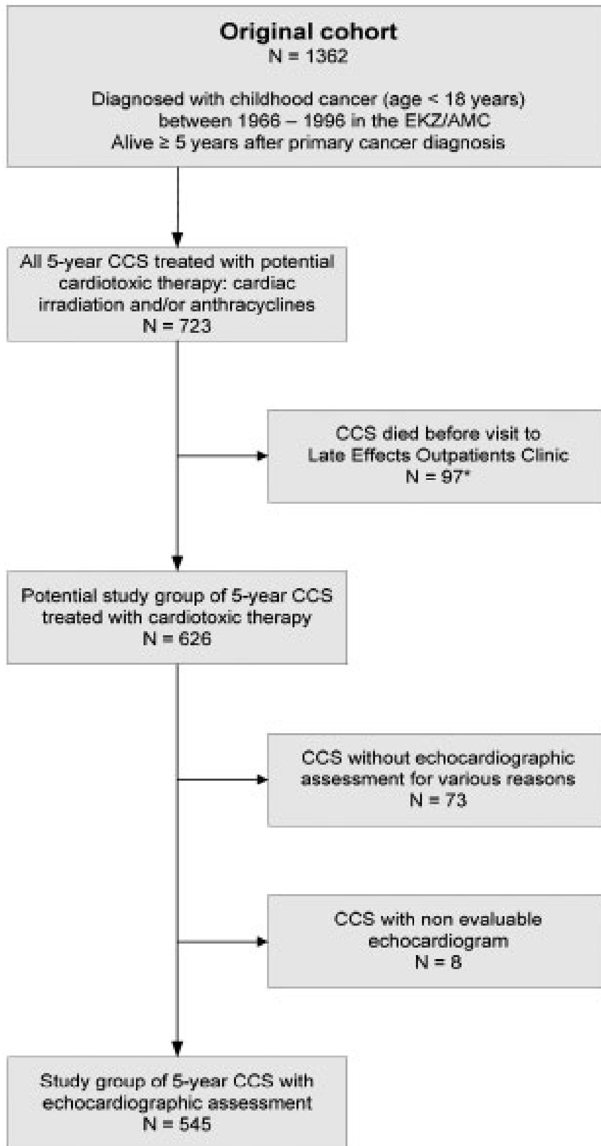

Figure 1. Flowchart of 5-year survivors of childhood cancer included in this study.
N number, *EKZ/AMC* Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands, *CCS* childhood cancer survivors
* None of the survivors died of valvular disease

echocardiogram for various reasons (e.g., emigration or refusal). Table 1 lists the characteristics of the cohort of eligible CCS, with and without evaluable echocardiograms. The groups did not differ by most potential determinants of valvular function, although there were slight differences in sex, and cumulative anthracycline dose.

Table 1. Patient characteristics of all eligible 5-year survivors of childhood cancer treated with radiotherapy involving the heart region and/or anthracyclines

Characteristic	All CCS with echocardiography *N* (%)	All CCS without (evaluable) echocardiography *N* (%)
Number	545 (100)	81 (100)
Sex		
Male	282 (51.7)	62 (76.5)
Female	263 (48.3)	19 (23.5)
Primary childhood cancer diagnosis		
ALL	108 (19.8)	12 (14.8)
ANLL	25 (4.6)	3 (3.7)
Hodgkin's disease	54 (9.9)	10 (12.3)
Non-Hodgkin's disease	111 (20.4)	19 (23.5)
Nephroblastoma	61 (11.2)	12 (14.8)
Soft tissue sarcoma	43 (7.9)	5 (6.2)
Ewing sarcoma	32 (5.9)	3 (3.7)
Osteosarcoma	46 (8.4)	6 (7.4)
CNS tumor	39 (7.2)	5 (6.2)
Germ cell tumor	9 (1.7)	2 (2.5)
Neuroblastoma	5 (0.9)	2 (2.5)
Other	12 (2.2)	2 (2.5)
Age at diagnosis of childhood cancer (years)		
Median (range)	7.6 (0.1-17.8)	7.8 (0.3-17.5)
0–4	181 (33.2)	29 (35.8)
5–9	179 (32.8)	21 (25.9)
10–14	143 (26.2)	22 (27.2)
15–18	42 (7.7)	9 (11.1)
Cardiotoxic treatment		
Anthracycline only* (± other therapy)†	364 (66.8)	48 (59.3)
Cardiac irradiation only‡ (± other therapy)†	109 (20.0)	24 (29.6)
Anthracycline & cardiac irradiation (± other therapy)†	72 (13.2)	9 (11.1)
Cardiac irradiation		
None	364 (66.8)	48 (59.3)
Any	181 (33.2)	33 (40.7)
Localization of cardiac irradiation		
Thorax[ǁ]	62 (34.3)	8 (24.2)
Abdomen[¶]	44 (24.3)	15 (45.5)
Spine	57 (31.5)	8 (24.2)
TBI	18 (9.9)	2 (6.1)
Cardiac irradiation dose in EQD_2 (Gy)(median; range)	24.2 (3.7-53.6)	24.8 (13.7-38.2)
Thorax[ǁ]	23.8 (9.5-53.6)	23.0 (17.6-36.7)
Abdomen[¶]	27.0 (3.7-39.6)	26.4 (15.8-38.2)
Spine	30.4 (15.0-50.1)	30.1 (13.7-34.1)
TBI	15.8 (14.0-21.6)	19.6 (17.6-21.6)
Unknown	5 (2.8)	2 (6.1)
Anthracyclines		
None	109 (20.0)	24 (29.6)

Table 1. Patient characteristics of all eligible 5-year survivors of childhood cancer treated with radiotherapy involving the heart region and/or anthracyclines *(continued)*		
Any	43 (80.0)	57 (70.4)
Cum anthracycline dose (mg/m^2)		
Median (range)	270 (40-750)	190 (25-575)
1-100	40 (9.2)	11 (19.3)
101-200	140 (32.1)	16 (28.1)
201-300	105 (24.1)	12 (21.1)
301-400	45 (10.3)	3 (5.3)
401-500	90 (20.6)	7 (12.3)
> 500	13 (3.0)	3 (5.3)
Dose unknown	3 (0.7)	5 (8.8)
Cyclophosphamide		
No	275 (50.5)	47 (58.0)
Yes	270 (49.5)	34 (42.0)
Ifosfamide		
No	472 (86.6)	72 (88.9)
Yes	73 (13.4)	9 (11.1)
Cisplatin		
No	502 (92.1)	77 (95.1)
Yes	43 (7.9)	4 (4.9)
Vincristine		
No	87 (16.0)	14 (17.3)
Yes	458 (84.0)	67 (82.7)
Recurrence since primary cancer diagnosis		
No	450 (82.6)	65 (80.2)
Yes	95 (17.4)	16 (19.8)

CCS childhood cancer survivor, *CTX* cardiotoxic treatment (i.e. anthracyclines and/or cardiac irradiation), *N* number, *ALL* acute lymphoblastic leukemia, *ANLL* acute non-lymphoblastic leukemia, *CNS* central nervous system, *Cum* cumulative, *TBI* total body irradiation, *EQD$_2$* equivalent dose in 2-Gray fractions, *Gy* Gray
*Anthracycline only includes treatment with anthracyclines and no radiotherapy involving the heart region, with or without all other treatment.
†Other therapy includes all other treatment except anthracyclines, radiotherapy involving the heart region or cardiac surgery.
‡Cardiac irradiation only is radiotherapy involving the heart region with no anthracycline and includes thoracic irradiation, abdominal irradiation, spinal irradiation and TBI.
‖Thorax includes radiotherapy to the left lung, mantle field, mediastinum and/or left axilla irradiation.
¶Abdomen includes radiotherapy to the left or whole abdomen, para-aortic lymph nodes, and inverted Y irradiation.

Valvular abnormalities, cumulative risks and associated risk factors

Overall, 169 of all 545 CCS (31.0%), and 78 of 181 (43.1%) CCS treated with radiotherapy to the heart region had one or more valvular abnormalities after a median follow-up time of 14.9 years (range 5.1-36.8) and at a median attained age of 22.0 years (range 7.0-49.7). Table 2 describes the echocardiographic measurements for all valves. Of all mild or higher graded abnormalities, the majority (194/225; 86.2%) was graded as mild. Most common valvular abnormalities were mild or higher severity tricuspid valve disorders (N=119; 21.8%) and mild or higher severity mitral valve disorders (N=73; 13.4%), including 1 mitral valve replacement.

Table 2. Echocardiographic assessment of valvular abnormalities in 5-year survivors of childhood cancer (*N*=545)

	Normal – Trace (%)	Mild (%)	Moderate (%)	Severe (%)	Overall mild or higher (%)	Unknown (%)*
Aortic valve					16 (2.9)	
AV regurgitation	480 (88.1)	9 (1.7)	4 (0.7)	1 (0.2)		51 (9.4)
AV stenosis	494 (90.6)	1 (0.2)	1 (0.2)	0		49 (9.0)
Mitral valve					73 (13.4)	
MV regurgitation	457 (83.9)	63 (11.6)	6 (1.1)	2 (0.4)		1 (3.1)
MV stenosis	494 (90.6)	1 (0.2)	1 (0.2)	0		49 (9.0)
Tricuspid valve					119 (21.8)	
TV regurgitation	369 (67.7)	106 (19.4)	12 (2.2)	1 (0.2)		57 (10.5)
TV stenosis	332 (60.9)	0	0	0		213 (39.1)
Pulmonary valve					17 (3.1)	
PV regurgitation	114 (20.9)	14 (2.6)	2 (0.4)	0		415 (76.1)
PV stenosis	120 (22.0)	0	1 (0.2)	0		424 (77.8)
Overall 1 or more valvular abnormalities mild or higher†					225/169 (31.0)	

N number, *AV* aortic valve, *MV* mitral valve, *TV* tricuspid valve, *PV* pulmonary valve
*Valves which were not mentioned in the echocardiographic report (unknown) were considered normal.
†Overall 169 childhood cancer survivors had 225 valvular abnormalities mild (grade 2), moderate (grade 3) or severe (grade 4), see Appendix for definitions.

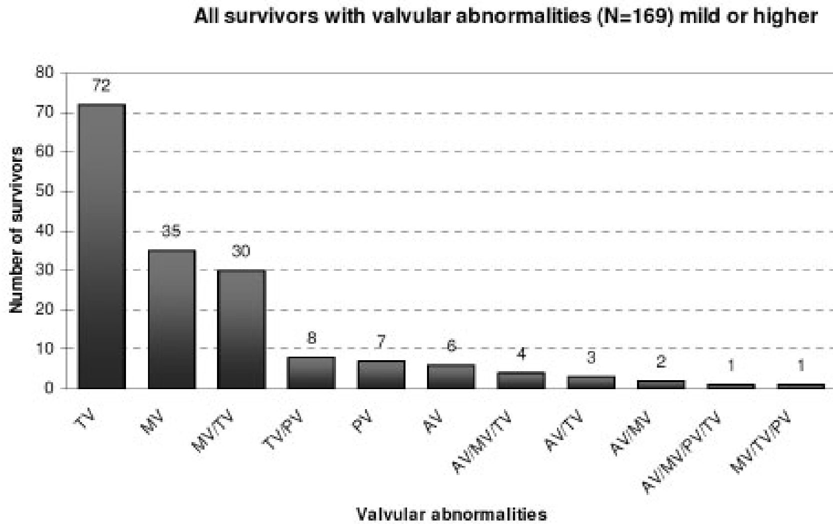

Figure 2. All 5-year survivors of childhood cancer with 1 or more non-physiological echocardiographic valvular abnormality.
N number, *TV* tricuspid valve, *MV* mitral valve, *PV* pulmonary valve, *AV* aortic valve

The prevalence of mild or higher severity aortic and pulmonary valve abnormalities were 16 (2.9%) and 17 (3.1%), respectively. Figure 2 shows the distribution of the 225 valvular abnormalities in 169 CCS (120 had one abnormality, 49 had two or more abnormalities).

The prevalence of grade mild and higher valve abnormalities was higher in irradiated survivors as compared with non-irradiated survivors for aortic (6.6% vs. 1.1%); mitral (19.9% vs. 10.2%) and tricuspid (29.3% vs. 18.1%) abnormalities, respectively; pulmonary abnormalities were similar in both groups (3.3% vs. 3.0%).

Table 3 describes the patient characteristics of all included 5-year CCS and CCS with valvular abnormalities. Twelve CCS had a congenital heart disease, mostly atrial and/or ventricular septum defects. Seven of those had a mild or higher valvular abnormality. Appendix Table 1 provides more details about these patients.

Table 4 presents the results from the two multivariable logistic regression models; model 1 quantifying the cumulative EQD_2, and model 2 the EQD_2 per radiation field. Higher EQD_2 (OR 1.33 per 10 Gy (95%CI:1.11-1.60, P=0.002)), older age at diagnosis (OR 1.05 (95%CI:1.00-1.10, P=0.04)), and CHD (OR 3.79 (95%CI:1.15-12.5, P=0.03)) were significantly associated with having any valvular abnormality. The risk of tricuspid valvular abnormalities was significantly associated with EQD_2 (OR 1.30 per 10 Gy (95%CI:1.07-1.58, P=0.008)), and the risk of mitral valvular abnormalities was significantly associated with both EQD_2 and congenital heart disease (OR 1.35 per 10 Gy (95%CI:1.07-1.69, P=0.01) and OR 4.11 (95%CI:1.14-14.9, P=0.03), respectively).

In model 2 the association between the risk of valvular abnormalities and the EQD_2 per radiation field was investigated. Both thoracic and TBI dose significantly increased the risk of any valvular abnormality (OR 1.48 per 10 Gy (95%CI:1.13-1.93, P=0.004) and OR 2.04 per

Table 3. Patient characteristics of all included 5-year survivors with and without echocardiographic valvular abnormalities

Characteristic	All CCS without valvular abnormalities	All CCS with valvular abnormalities	All CCS with TV abnormalities	All CCS with MV abnormalities	All CCS with PV abnormalities	All CCS with AV abnormalities
Number	376	169	119	73	17	16
LVSF (%)						
Median (range)	34.0 (7.1-62.5)	31.9 (14.0-50.0)	31.1 (16.2-45.8)	31.8 (14.0-50.0)	35.1 (20.4-43.6)	34.9 (22.2-40.4)
LVSF						
<30%	75 (19.9)	63 (37.3)	47 (39.5)	31 (42.5)	6 (35.3)	6 (37.5)
≥30%	298 (79.3)	106 (62.7)	72 (60.5)	42 (57.5)	11 (64.7)	10 (62.5)
Unknown	3 (0.8)	0	0	0	0	0
Cardiotoxic treatment						
Anthracycline only* (± other therapy)†	273 (72.6)	91 (53.8)	66 (55.5)	37 (50.7)	11 (64.7)	4 (25.0)
Cardiac irradiation only‡ (± other therapy)†	59 (15.7)	50 (29.6)	30 (25.2)	24 (32.9)	5 (29.4)	10 (62.5)
Anthracycline & cardiac irradiation (± other therapy)†	44 (11.7)	28 (16.6)	23 (19.3)	12 (16.4)	1 (5.9)	2 (12.5)
Anthracyclines						
None	59 (15.7)	50 (29.6)	30 (25.2)	24 (32.9)	5 (29.4)	10 (62.5)
Any	317 (84.3)	119 (70.4)	89 (74.8)	49 (67.1)	12 (70.6)	6 (37.5)
Cum anthracycline dose (mg/m^2)						
Median (range)	270 (50-750)	280 (40-420)	270 (40-720)	300 (50-720)	360 (150-450)	375 (120-500)
Cardiac irradiation						
None	273 (72.6)	91 (53.8)	66 (55.5)	37 (50.7)	11 (64.7)	4 (25.0)
Any	103 (27.4)	78 (46.2)	53 (44.5)	36 (49.3)	6 (35.3)	12 (75.0)
Cardiac irradiation dose in EQD_2 (Gy)						
Median (range)	22.9 (9.7-50.11)	25.0 (3.7-53.6)	26.2 (14.3-53.6)	27.0 (3.7-53.6)	23.5 (17.6-32.2)	25.0 (9.5-41.1)

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Table 3. Patient characteristics of all included 5-year survivors with and without echocardiographic valvular abnormalities *(continued)*

Localization of cardiac irradiation						
Thorax§	28 (27.2)	34 (43.6)	24 (45.3)	15 (41.7)	3 (50.0)	8 (66.7)
Abdomen‖	29 (28.2)	15 (19.2)	6 (11.3)	9 (25.0)	1 (16.7)	1 (8.3)
Spine	37 (35.9)	20 (25.6)	16 (30.2)	7 (19.4)	2 (33.3)	3 (25.0)
TBI	9 (8.7)	9 (11.5)	7 (13.2)	5 (13.9)	0	0
Follow-up since primary cancer diagnosis at cardiac assessment (years)						
Median (range)	14.0 (5.1-36.8)	16.3 (5.6-36.1)	16.3 (5.7-35.1)	17.1 (5.6-36.1)	16.0 (8.2-28.5)	21.5 (11.3-32.4)
Attained age at cardiac assessment						
Median (range)	21.1 (7.0-49.7)	23.4 (16.1-44.3)	22.9 (16.2-43.1)	24.0 (17.1-44.3)	22.7 (16.2-31.2)	29.4 (19.9-44.3)

CCS childhood cancer survivor *AV* aortic valve, *MV* mitral valve, *TV* tricuspid valve, *PV* pulmonary valve, *LVSF* left ventricular shortening fraction, *Cum* cumulative, EQD_2 equivalent dose in 2-Gray fractions, *Gy* Gray, *TBI* total body irradiation

*Anthracycline only includes treatment with anthracyclines and no radiotherapy involving the heart region, with or without all other treatment.

†Other therapy includes all other treatment except anthracyclines, radiotherapy involving the heart region or cardiac surgery.

‡Cardiac irradiation only is radiotherapy involving the heart region with no anthracycline and includes thoracic irradiation, abdominal irradiation, spinal irradiation and TBI.

‖Thorax includes radiotherapy to the left lung, mantle field, mediastinum and/or left axilla irradiation.

¶Abdomen includes radiotherapy to the left or whole abdomen, para-aortic lymph nodes, and inverted Y irradiation.

Table 4. Multivariable logistic regression analyses of potential determinants of echocardiographic valvular abnormalities

Determinant	All valvular abnormalities (*N*=169)		Tricuspid valve abnormalities (*N*=119)		Mitral valve abnormalities (N=73)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95%)	P
*Model 1**						
Sex (female vs. male)	1.24 (0.84-1.81)	.28	1.18 (0.77-1.79)	.45	1.25 (0.74-2.08)	.40
Age at diagnosis (per year)	1.05 (1.00-1.10)	.04	1.02 (0.97-1.07)	.51	1.04 (0.98-1.11)	.20
Anthracycline (per 100 mg/m^2)	1.08 (0.92-1.26)	.35	1.07 (0.90-1.26)	.44	1.21 (0.99-1.48)	.07
Cyclophosphamide (yes vs. no)	1.09 (0.67-1.76)	.73	1.14 (0.67-1.93)	.63	0.96 (0.50-1.87)	.91
Ifosfamide (yes vs. no)	1.00 (0.52-1.96)	.99	1.31 (0.65-2.65)	.45	0.97 (0.39-2.41)	.97
Vincristine (yes vs. no)	0.97 (0.51-1.85)	.94	0.99 (0.49-1.99)	.98	0.69 (0.32-1.51)	.36
Cisplatin (yes vs. no)	0.56 (0.20-1.53)	.26	0.61 (0.20-1.85)	.39	0.37 (0.09-1.63)	.19
RTX (EQD_2 per 10 Gy)†	1.33 (1.11-1.60)	.002	1.30 (1.07-1.58)	.008	1.35 (1.07-1.69)	.01
CHD (yes vs. no)	3.79 (1.15-12.5)	.03	0.79 (0.17-3.71)	.76	4.11 (1.14-14.9)	.03
*Model 2**						
Sex (female vs. male)	1.23 (0.84-1.81)	.30	1.17 (0.76-1.78)	.48	1.23 (0.73-2.06)	.44
Age at diagnosis (per year)	1.04 (0.99-1.09)	.09	1.00 (0.95-1.06)	.94	1.03 (0.97-1.10)	.32
Anthracycline (per 100 mg/m^2)	1.09 (0.93-1.27)	.29	1.11 (0.93-1.31)	.25	1.21 (0.98-1.49)	.07
Cyclophosphamide (yes vs. no)	0.97 (0.58-1.61)	.91	0.95 (0.54-1.66)	.86	0.83 (0.41-1.69)	.61
Ifosfamide (yes vs. no)	0.87 (0.43-1.73)	.68	1.05 (0.51-2.19)	.89	0.82 (0.32-2.09)	.67
Vincristine (yes vs. no)	0.94 (0.48-1.82)	.85	1.04 (0.51-2.13)	.92	0.64 (0.28-1.44)	.28
Cisplatin (yes vs. no)	0.56 (0.20-1.54)	.26	0.66 (0.22-2.03)	.47	0.36 (0.08-1.60)	.18
RTX thorax (EQD_2 per 10 Gy)†	1.48 (1.13-1.93)	.004	1.49 (1.14-1.96)	.004	1.45 (1.07-1.96)	.017
RTX abdomen (EQD_2 per 10 Gy)†	1.19 (0.89-1.61)	.24	0.93 (0.64-1.33)	.68	1.30 (0.91-1.87)	.16
RTX spine (EQD_2 per 10 Gy)†	1.22 (0.96-1.55)	.10	1.30 (1.00-1.67)	.046	1.15 (0.83-1.60)	.40
RTX TBI (EQD_2 per 10 Gy)†	2.04 (1.12-3.70)	.019	1.93 (1.05-3.55)	.03	2.34 (1.19-4.60)	.015
CHD (yes vs. no)	3.43 (1.02-11.6)	.046	0.65 (0.13-3.15)	.59	3.63 (0.98-13.4)	.053

N number, *OR* odds ratio, *CI* confidence interval, *P* p-value, *vs.* versus, EQD_2 equivalent dose in 2-Gy fractions, *Gy* Gray, *CHD* congenital heart disease, *RTX* radiotherapy, *TBI* total body irradiation
*corrected for time since primary cancer diagnosis until cardiac assessment.
†Radiotherapy is radiotherapy involving the heart region and includes thoracic irradiation, abdominal irradiation, spinal irradiation and TBI.
Radiotherapy categories (thorax, abdomen, spine and TBI) are mutually exclusive in Model 2.

10 Gy (95%CI:1.15-3.70, P=0.019), respectively). This was also the case for mitral valve abnormalities separately (OR 1.45 per 10 Gy (95%CI:1.07-1.96, P=0.017), and OR 2.34 per 10 Gy (95%CI:1.19-4.60, P=0.015), respectively). Effects of age at diagnosis and congenital heart disease did not change much. For tricuspid valve abnormalities, comparable associations with thoracic irradiation and TBI were found, as well as a significant association with spinal irradiation (OR 1.30 per 10 Gy (95%CI:1.05-3.55, P=0.03)).

In both models, anthracycline dose non-significantly increased the risk of mitral valve abnormalities (OR 1.21; 95%CI:0.99-1.48, P=0.07, and OR 1.21; 95%CI:0.98-1.49, P=0.07, respectively). There was no evidence of interaction between anthracyclines and EQD_2 when adding the interaction term to the model for any valvular abnormality, (OR 0.96; (95%CI:0.87-1.07, P=0.47)), and for mitral and tricuspid valve abnormalities (OR 0.97 (95%CI:0.85-1.10, P=0.61) and OR 1.02 (95%CI: 0.91-1.14, P=0.78), respectively). We also found no evidence of an interaction between EQD_2 and congenital heart disease when adding the interaction term to model 1 for any valvular abnormality, (OR 1.75; (95%CI:0.33-9.38, P=0.51)), and for mitral and tricuspid valve abnormalities (OR 0.63 (95%CI:0.17-2.26, P=0.48) and OR 4.40 (95%CI:0.50-39.0, P=0.18), respectively).

Discussion

In our study, we observed valvular abnormalities measured by echocardiography in 31% of 5-year CCS treated with potentially cardiotoxic therapy after a median follow-up of nearly 15 years and at a median attained age of 22 years. The most commonly observed abnormalities were those of the tricuspid (21.8%) and mitral (13.4%) valves. The majority (86.2%) of all abnormalities were mild. The risk of valvular abnormalities increased with higher irradiation dose. We confirmed that the presence of congenital heart disease was associated with a higher risk of valvular abnormalities, as previously shown in our study on symptomatic cardiac events.[7] We found no statistically significant evidence that sex, anthracyclines, or other chemotherapy agents played a role in the risk of valvular abnormalities. Older age at diagnosis was associated with the occurrence of more valvular abnormalities.

Evaluation of the cumulative irradiation dose and the dose per radiation field showed that thoracic and TBI dose were significantly associated with an increased risk of valvular abnormalities. Although not significant, this risk also seems to be increased after abdominal or spinal irradiation. Spinal irradiation significantly increased the risk of tricuspid valve abnormalities. A possible explanation is the localization of the tricuspid valve in front of the spine. Consequently, it will receive the highest dose of spinal irradiation as compared to the other valves.

The pathophysiology of valvular abnormalities after radiotherapy involving the heart region is not well understood and cannot be explained by microvascular damage, because the heart valves are avascular.[14] Most likely, irradiation injures the valve cusps or leaflets, causing thickening, fibrosis and calcification. Similarly, the chordae tendineae, which

control valve leaflet movements, can thicken and shorten.

Thus far, only a few studies have evaluated the risk of echocardiographic valvular disease in CCS with different definitions.[15,19] Hancock *et al* focused on cardiac disease in 635 children with Hodgkin's disease. They found six valvular abnormalities (0.9%); however, it is unclear if the ascertainment of asymptomatic disease was complete.[19] Adams *et al* showed that 42.6% of 48 childhood Hodgkin survivors had ≥1 valvular abnormality; all survivors had received mediastinal irradiation with a median dose of 40 Gy.[15] In our cohort 181 (33%) of the CCS received radiotherapy involving the heart region with a median dose of 25.0 Gy (24.2 Gy EQD_2), and 78 (43.1%) had a valvular abnormality. Furthermore, age at treatment differed from that in our study (median 16.5 versus 7.6 years), and echocardiographic variables were expressed as z-scores, whereas we graded abnormalities in a standard manner.[31-34]

Mulrooney *et al* investigated the risk of cardiac events, including symptomatic valvular disease in a large cohort of CCS, using questionnaires. They found a nearly 5-fold higher relative hazard of valvular abnormalities in CCS compared with sibling controls.[5] The prevalence of 1.6% of stiff or leaking heart valves in their study is largely similar to that of symptomatic valvular disease in our previous study.[7] The prevalence of asymptomatic valvular abnormalities in our present study is remarkably higher than the prevalence of symptomatic abnormalities as reported previously.[7]

Although the majority of identified valvular abnormalities in our study were mild, the prevalence is high as compared to healthy controls. The Framingham Heart Study showed prevalences of 0% for aortic, 9.2% for mitral, and 13.7% for tricuspid valvular abnormalities grade mild and higher in a group of 26-39 year old healthy men and women.[35] Pulmonary abnormalities were not evaluated. In the same age group at time of echocardiography (N=184) in our cohort, the prevalence of these respective outcomes was 4.9%, 21.2%, and 21.2%. Studies with longer follow-up are necessary to investigate whether the asymptomatic valvular abnormalities will worsen over time and if these survivors eventually develop symptomatic valvular disease.

In contrast to Mulrooney *et al*,[5] we found no significant evidence that treatment with (higher doses of) anthracyclines was associated with a higher risk of valvular disease. Likewise, there was no evidence that cyclophosphamide, ifosfamide, cisplatin or vincristine increased the risk of valvular abnormalities. Longer follow-up preferably with a control group may be needed to show effects of these agents. Other studies on mostly symptomatic valvular abnormalities in Hodgkin survivors included both children and adults, or only adults, and had different follow-up times.[16,20,22,23] They all identified significantly increased incidences of valvular abnormalities associated with radiotherapy involving the heart region. Heidenreich *et al* focused on asymptomatic cardiac disease in adults treated for Hodgkin's lymphoma with mediastinal irradiation. They showed a high prevalence of valvular abnormalities, defined as trace to severe, increasing with time after irradiation. Most prevalent was aortic valvular disease, whereas we mainly identified tricuspid and mitral valve abnormalities.[20] The differences in findings may be due to the study population, our

cohort being treated in childhood, and the use of other radiation fields (and doses) besides the mediastinum.

Strengths of our study are the limited risk of selection bias as we were able to evaluate echocardiographic valvular abnormalities in a near complete cohort of CCS, and the limited risk of detection bias, as all echocardiographic measurements were performed in one institute by using the same screening protocol by cardiologists blinded for the specific treatments received by CCS. Additionally, we succeeded in retrieving complete and detailed treatment data, including cumulative anthracycline doses and irradiation doses. Our study also has limitations, such as the inability to examine the course of valvular disorders over time. This will be the focus of our next study. Furthermore, we did not have echocardiographic assessment of CCS not treated with cardiotoxic treatment, and due to the small number of aortic and pulmonary valve disorders we could not analyze these specific conditions. Additionally, we could not compare the prevalence of valvular abnormalities to that of the general Dutch population, as those figures are not available. However, we have compared CCS aged 26-39 years at time of echocardiography with healthy controls in the same age group from the Framingham Heart Study. Lastly, we might have underestimated the risk of developing valvular abnormalities, as we defined valves which were not mentioned in the echocardiographic report as normal. Future studies should focus on the clinical consequences, progression over time, and evaluation of benefits and risks of early detection and treatment of valvular abnormalities in CSS treated with radiotherapy involving the heart region.

In conclusion, 31.0% of 5-year CCS treated with potentially cardiotoxic therapy and 43.1% of the CCS treated with radiotherapy to the heart region had one or more echocardiographic valvular abnormalities at their first echocardiographic evaluation at our Outpatient Clinic for Late Effects of Treatment for Childhood Cancer. The risk of valvular abnormalities increased with higher irradiation dose. The presence of congenital heart disease was also associated with the risk of valvular abnormalities. We found no statistically significant evidence for anthracyclines or other chemotherapeutic agents to increase the risk of valvular abnormalities.

Long-term follow-up studies are necessary to investigate whether the asymptomatic valvular abnormalities will worsen over time and if these survivors eventually develop symptomatic valvular disease.

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Appendix

Calculation of EQD_2

In our study, we converted the physical radiation dose into the equivalent dose in fractions of 2 Gray (Gy) (EQD_2)[7] by using the formula: $EQD_2 = D*(d+\alpha/\beta)/(2+\alpha/\beta)$. In this formula, D represents the total dose given in fractions of d Gy. The value of the α/β ratio depends on the tissue under consideration; we used an α/β ratio of 3 Gray for late responding tissues. The EQD_2 includes both total dose and fractionation size size, and is considered to be appropriate to evaluate late radiation-induced effects, because the fractionation size is important in determining late effects.[30] Another advantage is that EQD_2 values enable us to compare diverse fractionation schedules in a uniform way.[30] The EQD_2 is expressed in Gy. All calculated EQD_2s embody the maximum applied dose per treatment localization.

For our cohort the median physical doses were as follows: 24.8 Gy (range 10.8-55.8 Gy) for 58 of 62 survivors treated with thoracic radiation, 30.0 Gy (range 4.5-42.0 Gy) for 43 of 44 survivors treated with abdominal radiation, 34.5 Gy (range 17.5-52.2 Gy) for all 57 survivors who had spinal radiation, and 7.5 Gy (range 7.0-12.0 Gy) for all of the 18 with TBI treated survivors.

Cardiac assessment

The cardiac assessment included standardized M-mode and two-dimensional echocardiography with a concurrent electrocardiogram for the measurement of the left ventricular fractional shortening and for color and pulsed Doppler studies of the valvular functions. All examinations were performed using commercially available ultrasound scanners. Auscultation of the heart was not included in this assessment, as it has been shown to have a limited specificity and a low positive predictive value.[20]

Valvular function was assessed as follows: mitral and tricuspid valvular regurgitation were visually graded using a scale from trace, mild, moderate to severe regurgitation, equivalent to the ratio of the color Doppler-jet area to the atrial area (extending <1 cm into the atrium as trace, <20% with a jet extension of at least 1 cm into the atrium as mild, 20% to 40% as moderate, and >40% as severe).

Regurgitation leading to reversal in the hepatic (tricuspid regurgitation) or pulmonary (mitral regurgitation) veins was also considered severe. Aortic regurgitation was visually graded using the ratio of the width of the color jet at the site of the valve leaflets to the diameter of the left ventricle outflow tract (LVOT) (<1/4 as trace, between 1/4 and 1/2 as mild, between 1/2 and 2/3 as moderate, and >2/3 as severe). Pulmonary regurgitation was visually graded using color jet extension into the right ventricle outflow tract (RVOT) (small jet <1 cm as trace, jet <2 cm as mild, jet far in RVOT as moderate, and severe with the pulmonary regurgitation flow visible coming from the arteria pulmonalis branches).

Aortic stenosis was considered absent if the peak-pressure-difference over the aortic valve was <15 mmHg, mild if the difference was 15-40 mmHg, moderate if the difference was

between 40-70 mmHg and severe if the difference was 70-100 mmHg. Pulmonary stenosis was considered trace if the peak-pressure-difference was <15 mmHg, mild if the difference was 15-40 mmHg, moderate pulmonary stenosis if the difference was 50-80 mmHg, and severe if the difference was >80 mmHg. Mitral and tricuspid stenosis were considered severe if the hemodynamic ostium-area was <1.0 cm^2, moderate if it was between 1.0-1.5 cm^2, mild if it was between 1.5-2.2 cm^2. Aortic and mitral valve thickening was considered present if the motions of the valve leaflets were restricted. Calcifications and valve thickening were scored under stenosis, depending on severity. If there were no data in the report about the aortic, tricuspid, mitral and/or pulmonary valve, they were considered to be normal, as it is unlikely that (anatomic) abnormalities were not mentioned by protocol.[31-34]

The LVFS was calculated using the formula:
LVFS(%) = ((LVDD–LVDS)/LVDD)*100%, where LVDD is the left ventricular diastolic diameter measured at the start of the QRS complex and LVDS is the left ventricular systolic diameter. LVFS was considered deviate if it was less than 30%.[32] Echocardiographic measurements were performed by trained echocardiography technicians, and approved and interpreted by experienced cardiologists.

Appendix Table 1. Valvular abnormalities in 5-year survivors of childhood cancer with cardiac assessment and congenital heart disease*

	Survivors with congenital heart disease†		
	Without valvular abnormalities	With valvular abnormalities	Total
ASD	2	2	4
VSD	2	1	3
ASD & VSD	0	1	1
Bicuspid aortic valve	1	3	4
Total	5	7	12

ASD atrial septum defect, *VSD* ventricular septum defect
*Data are numbers
†Including 4 survivors with Down syndrome (2 with ASD, 1 with ASD and VSD and 1 with bicuspid aortic valve)

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