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Presence and utility of electrocardiographic abnormalities in long-term childhood cancer survivors

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ABSTRACT

Background We assessed the prevalence and diagnostic value of ECG abnormalities for cardiomyopathy surveillance in childhood cancer survivors.

Methods In this cross-sectional study, 1381 survivors (≥5 years) from the Dutch Childhood Cancer Survivor Study part 2 and 272 siblings underwent a long-term follow-up ECG and echocardiography. We compared ECG abnormality prevalences using the Minnesota Code between survivors and siblings, and within biplane left ventricular ejection fraction (LVEF) categories. Among 880 survivors who received anthracycline, mitoxantrone or heart radiotherapy, logistic regression models using least absolute shrinkage and selection operator identified ECG abnormalities associated with three abnormal LVEF categories (<52% in male/<54% in female, <50% and <45%). We assessed the overall contribution of these ECG abnormalities to clinical regression models predicting abnormal LVEF, assuming an absence of systolic dysfunction with a <1% threshold probability.

Results 16% of survivors (52% female, mean age 34.7 years) and 14% of siblings had major ECG abnormalities. ECG abnormalities increased with decreasing LVEF. Integrating selected ECG data into the baseline model significantly improved prediction of sex-specific abnormal LVEF (c-statistic 0.66 vs 0.71), LVEF <50% (0.66 vs 0.76) and LVEF <45% (0.80 vs 0.86). While no survivor met the preset probability threshold in the first two models, the third model used five ECG variables to predict LVEF <45% and was applicable for ruling out (sensitivity 93%, specificity 56%, negative predictive value 99.6%). Calibration and internal validation tests performed well.

Conclusion A clinical prediction model with ECG data (left bundle branch block, left atrial enlargement, left heart axis, Cornell's criteria for left ventricular hypertrophy and heart rate) may aid in ruling out LVEF <45%.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the general population, ECG measures are used for risk stratification for heart failure. In childhood cancer survivors, various ECG abnormalities occur after cardiotoxic treatment, some of which can be of clinical relevance. The diagnostic performance of conventional ECG abnormalities for decreased left ventricular ejection fraction (LVEF) in survivors at risk of cardiomyopathy has not been evaluated yet.

WHAT THIS STUDY ADDS

⇒ Major ECG abnormalities occur in 16% of survivors, increasing with severity of cardiac dysfunction.

⇒ The use of conventional ECG in at-risk survivors is inadequate to detect or exclude mild systolic dysfunction defined as LVEF <54/52% or as LVEF <50%.

⇒ The use of conventional ECG in at-risk survivors may help primarily to exclude therapeutically relevant systolic dysfunction (LVEF <45%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A triage strategy for regular cardiomyopathy surveillance starting with ECG measures may help to reduce the number of screening echocardiograms, with minimal risk of missing survivors with a therapeutically relevant LVEF.

BACKGROUND

Childhood cancer survivors (hereafter, 'survivors') treated with anthracyclines, mitoxantrone or radiation involving the heart region (hereafter, 'heart RT') have an increased risk of cardiovascular diseases which lead to an increased risk of morbidity and mortality compared with the general population.[1]

Cardiomyopathy surveillance with echocardiography is an important part of cardiac care for survivors who are at risk.[2] The main goal is to detect myocardial dysfunction before heart failure occurs to prevent or slow down progression with heart failure medication. One of the two globally used guidelines on long-term follow-up for cardiomyopathy recommends performing ECG examination 5 years after cancer diagnosis as a baseline recording and thereafter on indication.[2 3] However,

the precise role and added value of ECG abnormalities in the surveillance of cardiomyopathy remain unclear.[4]

Our recent systematic review in ≥2-year survivors demonstrated that various ECG abnormalities occur after cardiotoxic treatment, some of which can be of clinical relevance. However, reports on clearly defined ECG abnormalities are sparse.[5] The Minnesota Code, a standardised coding system to support universal interpretation of ECG abnormalities in population studies, provides a systematic and transparent method to define ECG abnormalities.[6] In large cohort studies from the general population, it was demonstrated that certain ECG abnormalities predict future cardiac events including heart failure.[7–9] In survivors, the presence of major ECG abnormalities has been shown to be predictive of overall mortality.[10]

In other populations, ECG variables have been tested for the diagnosis of left ventricular (LV) systolic dysfunction with a sensitivity up to 98% but with varying and usually lower specificity.[11 12] The sensitivity and negative predictive values may however be influenced by different definitions of LV dysfunction and ECG abnormalities and the prior probability of LV dysfunction. The 2021 European Society of Cardiology guideline advocates the diagnostic use of ECG in combination with natriuretic peptide testing in patients with suspected chronic heart failure, where a normal ECG and normal B-type natriuretic peptide make the diagnosis of heart failure highly unlikely, but in case of abnormality, an echocardiogram is still needed for ruling in purposes.[13] In survivors at risk of cardiotoxicity, the diagnostic performance of conventional ECG abnormalities for LV dysfunction has not been evaluated yet.

In this cross-sectional cardiac substudy of the Dutch Childhood Cancer Survivor Study (DCCSS), we aimed to study the prevalence of ECG abnormalities and whether a composite of ECG abnormalities would add value to a diagnostic model of LV dysfunction, as prediction models for heart failure and LV dysfunction based on cardiotoxic treatment doses already exist in survivors.[1]

METHODS

Study population

This cardiac substudy is part of the cross-sectional DCCSS LATER cohort (1963–2001) part 2; it focuses on early detection of subclinical cardiac dysfunction by different surveillance modalities.[14 15] In short, the study comprised ≥5-year survivors from multiple Dutch centres who have been treated with well-known cardiotoxic therapy (anthracyclines, mitoxantrone and/or heart RT) or potentially cardiotoxic cancer treatment (cyclophosphamide (intravenous), ifosfamide or vincristine without anthracyclines, mitoxantrone and/or heart RT). All survivors who were diagnosed with childhood cancer at age <18 years between 1 January 1963 and 31 December 2001 who received one of these treatments, and were alive and had a known address in the Netherlands were eligible. We excluded participants who had a heart transplant, had a severe congenital heart disease or were pregnant at the time of the study. Sibling controls, reflecting the general population with shared background, were enrolled as the optimal reference group. Siblings were recruited from the entire cohort without any matching procedure. Eligible survivors and siblings visited our late-effects clinic between February 2016 and February 2020 for usual care (including surveillance for hypertension, hypercholesterolaemia or diabetes) and/or research tests.

Data collection

We extracted patient and cancer treatment characteristics from the DCCSS LATER registry. For alkylating agents and anthracyclines, we used an equivalent ratio to calculate the dose.[16 17] Mitoxantrone, an anthraquinone with large cardiotoxic potential,[16] was not included in the anthracycline dose. We estimated radiotherapy dose received by the heart with a standardised protocol (see online supplemental file A). Participants provided information about their medical history, cardiovascular risk factors and medication use through questionnaires and during visits to outpatient clinics. Self-reported history of heart failure, myocardial infarction, arrhythmia, arterial hypertension and diabetes was validated against use of appropriate medication.

All participants underwent physical examination, 12-lead resting ECG examination and echocardiography. Trained observers were blinded for the clinical characteristics and manually analysed the ECGs under a standardised protocol including quality assessment. In case of unacceptable quality, we excluded the specific lead(s) for further analysis. We used the Minnesota Code to define ECG abnormalities (online supplemental file A).[6] Major ECG abnormalities were reported regardless of the presence of minor abnormalities. Minor abnormalities were reported without adjusting for the presence of a major abnormality. We excluded two minor Minnesota Codes (7–10 and 9–7), because these codes have been replaced by new criteria.[18] In addition, we evaluated heart rate, QRS duration and QTc duration as continuous variables and Cornell's criteria for LV hypertrophy (R wave in aVL+S in V3 >20 mm in females and >28 mm in males), as these have been associated with heart failure.[9 19 20] Systolic LV dysfunction was assessed by biplane LV ejection fraction (LVEF) on echocardiography.[21] To evaluate at which level of systolic dysfunction ECG abnormalities would contribute to their identification, we studied three LVEF categories: <52% (males)/<54% (females), <50% and <45%. The number of survivors with LVEF <40% was too low to allow for meaningful analysis.

Statistical analysis

The prevalence of ECG abnormalities was calculated in all survivors and separately in each of the (potentially) cardiotoxic cancer treatment groups. The results were compared with those of siblings, using the Fisher's exact test. We used multivariable logistic regression to adjust for differences in age and sex. For continuous ECG measures, medians were compared between survivors and siblings with the Wilcoxon signed-rank test.

For analysing LV systolic dysfunction prediction in a cardiomyopathy surveillance population, we selected survivors who received cardiotoxic treatments (anthracyclines, mitoxantrone and/or heart RT), without prior cardiomyopathy or pacemaker diagnosis. Using multivariable logistic regression models, we assessed the association between ECG variables and LV systolic dysfunction. Applying LASSO (least absolute shrinkage and selection operator) binary logistic regression, we identified the most effective discriminating predefined ECG abnormalities and continuous ECG measures for each of the LV dysfunction categories. We then added the selected ECG data to the baseline model including sex, age at diagnosis, age at ECG examination and treatment with anthracyclines, mitoxantrone and heart RT, known risk factors for cardiotoxicity.[1] To increase the statistical power of the model, we manually excluded non-contributing ECG data and merged the significant ECG abnormalities into a binary variable 'abnormal ECG based on LASSO analysis'.

To evaluate the potential added diagnostic value of ECG in cardiomyopathy surveillance, we quantified the discriminative ability of the models for each of the three categories of LV

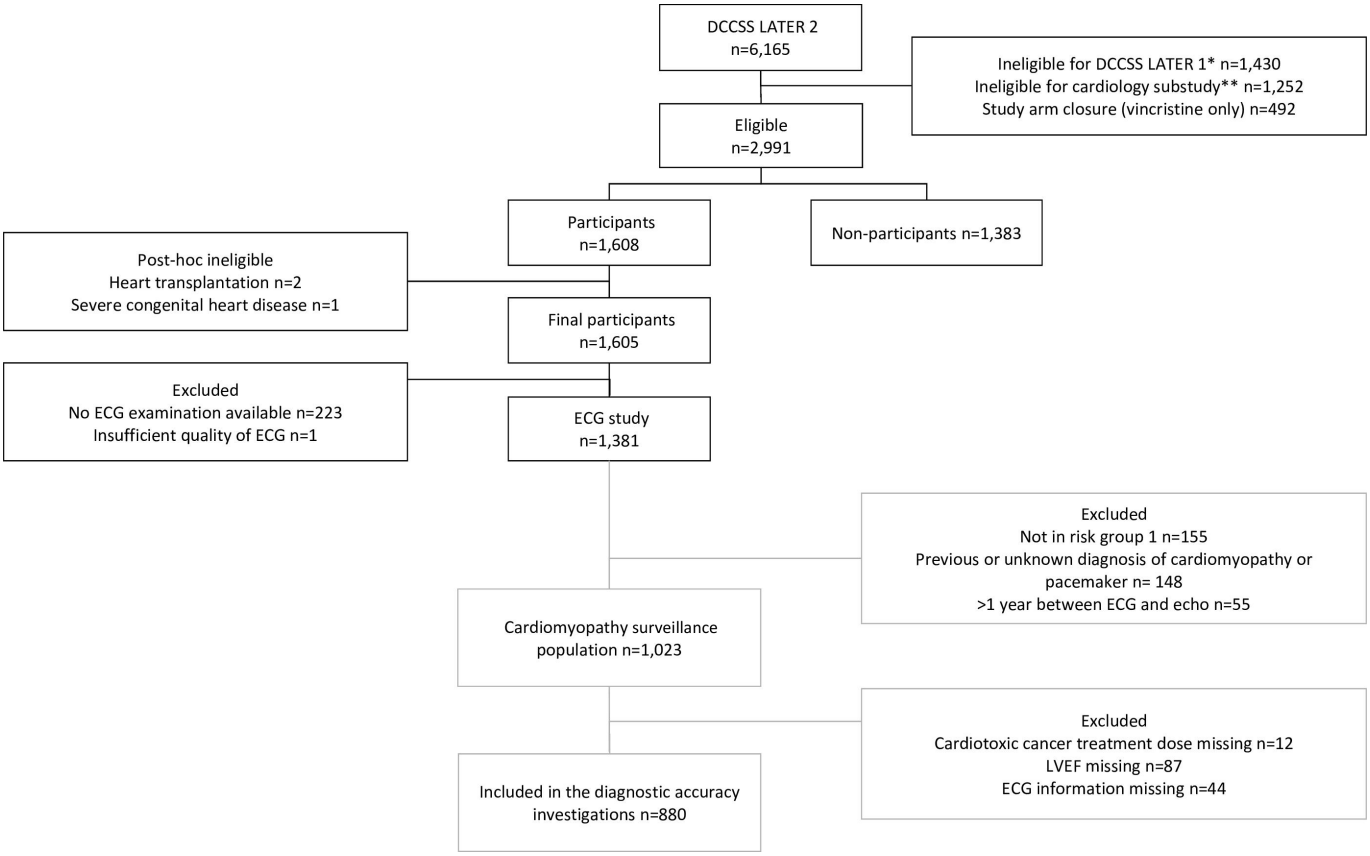

Figure 1 Flow chart of the study. *Examples of ineligibility criteria include: refusal of study participation, deceased, lost to follow-up and living abroad. **Survivors who did not fall into one of the following risk groups: risk group 1 survivors who received anthracyclines, mitoxantrone or chest-directed radiotherapy; risk group 2 (max n=100): cyclophosphamide only (no anthracyclines, mitoxantrone, or chest-directed radiotherapy, ifosfamide or vincristine); risk group 3 (max n=100): ifosfamide only (no anthracyclines, mitoxantrone, or chest-directed radiotherapy, cyclophosphamide or vincristine); risk group 4 (max n=100): vincristine only (no anthracyclines, mitoxantrone, or chest-directed radiotherapy, ifosfamide or cyclophosphamide).[25] DCCSS LATER 2, Dutch Childhood Cancer Survivor Study, LATER cohort (1963–2001) part 2; LVEF, left ventricular ejection fraction; n, number.

dysfunction with and without ECG abnormalities by the c-statistic and tested the calibration with the Hosmer-Lemeshow statistics (dividing the data into 10 groups).[22] We applied an estimated probability of <1% to assume absence of systolic dysfunction and calculated the diagnostic accuracy of the best discriminating models. This threshold for ruling out heart failure was introduced based on a clinically acceptable probability of false-negative diagnoses, as this percentage is close to the prevalence of heart failure in the European population aged 18–60 years.[23] Lastly, we validated the c-statistic of the final model with a bootstrap analysis (1000 resamples, R packages rms). SPSS (V.26) and R V.4.0.3 were used for statistical analysis, and a p value of <0.05 was considered statistically significant.

RESULTS

Study population

Figure 1 shows the inclusion flow chart of this study with 1381 survivors (52% female). Leukaemia (41%), lymphoma (24%) and renal tumours (12%) were the most frequent childhood cancers (table 1). For survivors, the median age at cancer diagnosis was 6.2 years (IQR 3.2–11.3), the median time since cancer diagnosis was 26.9 years (IQR 21.5–34.4) and the median age at ECG evaluation was 34.7 years (IQR 28.5–42.1). For siblings (n=272), the median age at ECG evaluation was 36.8 years (IQR 29.2–43.7). Most of the survivors (76%) received anthracyclines with a median dose of 180 mg/m^2 (IQR 120–288), and 71 survivors (5%) received mitoxantrone. One-third of the survivors received heart RT with a median prescribed dose of 12 Gray (IQR 3.5–20.5). There were 294 (21%) survivors with LVEF <54% in females and <52% in males, compared with 13 (5%) siblings. There were 148 (12%) survivors with LVEF <50%, 57 (5%) survivors with LVEF <45% and 11 survivors with LVEF <40%. Online supplemental file B shows the details of the participating and non-participating survivors concerning the cardiology project of the DCCSS LATER 2.

Prevalence of ECG abnormalities and association with LV systolic function

Major ECG abnormalities occurred in 16% of the survivors and in 14% of the siblings (p value adjusted for sex and age>0.05). Differences in prevalence became more apparent after we divided the survivors into different cardiotoxic cancer treatment exposure groups (figure 2). The prevalence of major ECG abnormalities was 12% in the survivors who received only potentially cardiotoxic therapy, 14% in those who received anthracyclines/mitoxantrone only and 18% in those who received anthracyclines/mitoxantrone and heart RT. The survivors who received heart RT only had a prevalence of 24% major ECG abnormalities. This latter group of survivors received the highest heart RT doses (table 1).

Table 1 Characteristics of the analysed survivors and siblings

	Survivors					Siblings
	All survivors n=1381*	Only anthracyclines/ mitoxantrone n=809	Only heart RT n=158	Heart RT and anthracyclines/ mitoxantrone n=253	Potentially cardiotoxic therapy n=155	n=272
Demographics, diagnosis and treatment history						
Sex, n (%)						
Female	719 (52)	379 (47)	83 (53)	116 (46)	83 (54)	162 (60)
Age at diagnosis, years, median (IQR)	6.2 (3.2–11.3)	6.3 (3.1–11.4)	6.9 (2.9–9.8)	6.9 (3.8–12.2)	4.1 (2.6–8.3)	
0–<5	572 (41)	322 (40)	66 (42)	95 (38)	87 (56)	
5–<10	397 (29)	236 (29)	54 (34)	68 (27)	36 (23)	
10–<15	322 (23)	194 (24)	31 (20)	69 (27)	27 (17)	
15–18	90 (7)	57 (7)	7 (4)	21 (8)	5 (3)	
Primary cancer diagnosis, n (%)						
Leukaemias	559 (41)	358 (44)	18 (11)	88 (35)	92 (59)	
Lymphomas/ reticuloendothelial	334 (24)	228 (28)	25 (16)	63 (25)	16 (10)	
CNS, intracranial and intraspinal neoplasms	46 (3)	3 (0.4)	35 (22)	1 (0.4)	6 (4)	
Neuroblastoma and other peripheral nervous cell tumours	43 (3)	19 (2)	16 (10)	8 (3)	1 (1)	
Retinoblastoma	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (1)	
Renal tumours	165 (12)	41 (5)	44 (28)	61 (24)	19 (12)	
Hepatic tumours	11 (1)	11 (1)	0 (0)	0 (0)	0 (0)	
Bone tumours	118 (9)	92 (11)	5 (3)	20 (8)	1 (1)	
Soft tissue and other extraosseous sarcomas	69 (5)	52 (6)	4 (3)	11 (4)	2 (1)	
Germ cell tumours	28 (2)	4 (1)	7 (4)	1 (0.4)	16 (10)	
Others	7 (1)	1 (0.1)	5 (3)	0 (0)	1 (1)	
Age at follow-up, years, median (IQR)	34.7 (28.5–42.1)	32.9 (27.5–39.8)	45.8 (38.0–50.3)	35.5 (30.9–41.0)	34.3 (25.7–43.5)	36.8 (29.2–43.7)
15–<25, n (%)	187 (14)	129 (16)	3 (2)	18 (7)	37 (24)	36 (13)
25–<35	521 (38)	347 (43)	25 (16)	102 (40)	43 (28)	90 (33)
35–<45	432 (31)	239 (30)	45 (29)	99 (39)	48 (31)	88 (32)
≥45	241 (18)	94 (12)	85 (54)	34 (13)	27 (17)	58 (21)
Time since cancer diagnosis, years, median (IQR)	26.9 (21.5–34.4)	25.6 (21.0–31.0)	40.1 (29.2–44.0)	27.3 (22.2–33.7)	30.7 (19.6–35.8)	
10–<20, n (%)	264 (19)	169 (21)	11 (7)	38 (15)	45 (29)	
20–<30	580 (42)	404 (50)	29 (18)	115 (46)	29 (19)	
30–<40	402 (29)	213 (26)	38 (24)	90 (36)	58 (38)	
≥40	135 (10)	23 (3)	80 (51)	9 (4)	22 (14)	
Cumulative anthracycline dose†, mg/m^2, median (IQR)	180 (120–288)	180 (120–288)		200 (150–299)		
No anthracyclines, n (%)	336 (24)	20 (3)	158 (100)	3 (1)	155 (100)	
1–100	174 (13)	138 (17)		36 (14)		
100.1–250	551 (40)	425 (53)		125 (49)		
>250	314 (23)	222 (28)		89 (35)		
Missing	6	4		0		
Mitoxantrone dose, mg/ m^2, median (IQR)	40 (20–72)	44 (20–93)		20 (20–50)		
No mitoxantrone, n (%)	1308 (95)	755 (94)		234 (93)	155 (100)	
1–40	40 (3)	26 (3)		14 (6)		

Continued

Table 1 Continued

	Survivors					Siblings
	All survivors n=1381*	Only anthracyclines/ mitoxantrone n=809	Only heart RT n=158	Heart RT and anthracyclines/ mitoxantrone n=253	Potentially cardiotoxic therapy n=155	n=272
>40	31 (2)	26 (3)		5 (2)		
Missing	2 (0.1)	2		0		
RT including the heart region dose, Gy, median (IQR)	12 (3.5–20.5)		14 (3–20)	10 (5–21)		
No RT including the heart region, n (%)	965 (70)	809 (100)	0 (0)	0 (0)	155 (100)	
1–15	260 (19)		82 (54)	177 (70)		
15.1–30	98 (7)		56 (37)	41 (16)		
>30	50 (4)		15 (10)	35 (14)		
Missing	8 (1)		5	0		
Vincristine exposed, n (%)	1153 (70)	690 (85)	237 (94)	102 (65)	118 (76)	
Ifosfamide exposed, n (%)	207 (15)	109 (14)	5 (3)	77 (30)	14 (9)	
Cyclophosphamide exposed, n (%)	774 (57)	552 (68)	39 (30)	157 (62)	23 (15)	
Outpatient clinic data, median (IQR)						
Waist circumference, cm	86 (78–94)	85 (78–94)	88 (80–97)	83 (75–90)	88 (81–96)	86 (80–95)
Systolic blood pressure, mm Hg	121 (112–132)	120 (112–129)	130 (118–142)	119 (110–131)	122 (112–134)	119 (109–128)
Diastolic blood pressure, mm Hg	75 (68–81)	74 (68–81)	78 (72–84)	75 (68–81)	75 (67–82)	73 (66–79)
Impaired LVEF at evaluation‡	294 (21)	160 (22)	31 (23)	84 (38)	16 (14)	13 (5)
Severe impaired LVEF at evaluation§	57 (5)	36 (5)	4 (3)	17 (8)	0 (0)	0 (0)
Questionnaire data, n (%)						
Ever smoked >1 year¶	377 (27)	231 (31)	43 (28)	67 (29)	35 (24)	79 (37)
Hypertension**	82 (6)	32 (4)	27 (18)	14 (6)	9 (6)	2 (1)
Use of lipid-lowering medication	57 (4)	16 (2)	18 (11)	16 (6)	7 (5)	1 (0.4)
Diabetes**	26 (3)	8 (1)	9 (6)	7 (3)	2 (1)	0 (0)
Arrhythmia**	16 (1)	7 (1)	6 (4)	3 (1)	0 (0)	0 (0)
Myocardial infarction**	4 (0.3)	1 (0.1)	1 (1)	2 (1)	0 (0)	0 (0)
Heart failure**	48 (4)	27 (4)	4 (3)	17 (7)	0 (0)	0 (0)
Cardiac surgery	23 (2)	8 (1)	8 (5)	5 (2)	2 (1)	0 (0)
Congenital heart disease	26 (2)	18 (2)	2 (1)	2 (1)	4 (3)	2 (1)

*In six survivors, the cardiotoxic cancer treatment was unclear due to missing information on either anthracycline exposure or heart RT.
†Calculated as doxorubicin+daunorubicin×0.5+epirubicine×0.8+idarubicine×3.
‡Defined as LVEF below normal threshold <54% (females) or <52% (males). Missing in 198.
§Defined as LVEF <45%. Missing in 198.
¶Composite of DCCSS LATER Study parts 1 and 2. Missing in 164.
**Self-reported and validated against appropriate medication use. Questionnaire data missing in 111 for hypertension, in 106 for diabetes, in 114 for arrhythmia, in 106 for myocardial infraction.
CNS, central nervous system; DCCSS LATER, Dutch Childhood Cancer Survivor Study LATER cohort (1963–2001); LVEF, left ventricular ejection fraction; n, number; RT, radiotherapy.

Minor ECG abnormalities were detected in 57% of the survivors vs 50% of the siblings (p value adjusted for sex and age>0.05). The prevalence was again the highest among survivors who received heart RT only (67%). Online supplemental file C shows the prevalence of the separate major, minor and other ECG abnormalities in survivors (and cardiotoxicity categories) and siblings.

For survivors exposed to cardiotoxic treatments, the prevalence of the individual ECG abnormalities is shown by the LVEF categories in online supplemental file D, table 2; most of them

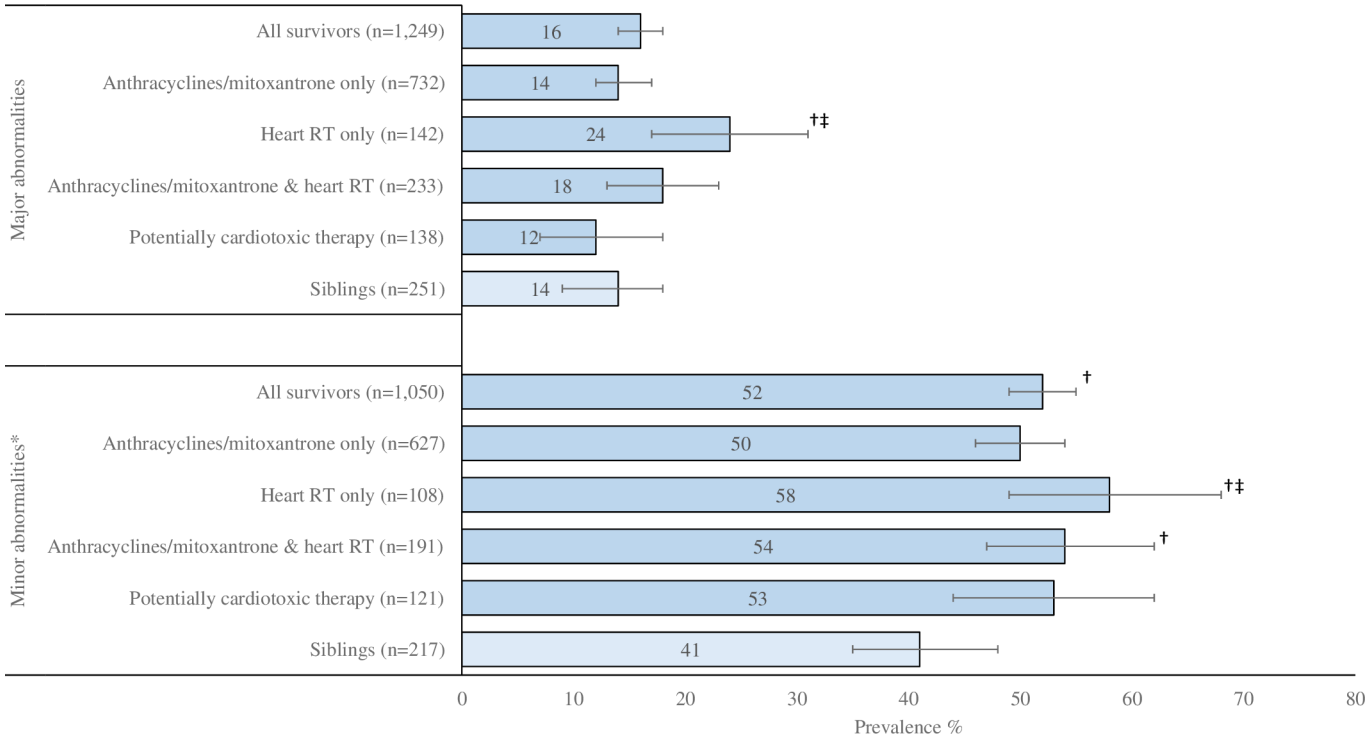

Figure 2 Prevalence of any major and minor ECG abnormalities. Comparison of the prevalence of any major and minor ECG abnormalities between survivors (all and per cardiotoxic cancer exposure) and siblings, both adjusted and unadjusted for sex and attained age. †Fisher's exact test demonstrated a p value of <0.05. ‡Comparison with siblings, adjusted for sex and age at ECG, demonstrated a p value of <0.05. RT, radiotherapy.

were comparable between the survivors with LVEF ≥52/54% and LVEF 45–52/54%, while the prevalence was significantly increased in survivors with LVEF <45%.

The added diagnostic value of ECG

For this part of the study, we evaluated the 880 survivors who were exposed to cardiotoxic cancer treatment with available dose, ECG and LVEF data. Of the survivors excluded due to previous or unknown diagnosis of cardiomyopathy/pacemaker, n=66 had LVEF <54/52%.

The baseline model contained the variables sex, age at diagnosis, age at ECG examination and treatment with anthracyclines, mitoxantrone and heart RT. When integrating selected ECG data, the model significantly improved compared with the baseline model with all predefined outcome measures (LVEF <54/52%, LVEF <50% and LVEF <45%) (p<0.001). For LVEF <54/52%, the c-statistic increased from 0.66 (95% CI 0.61 to 0.70) to 0.71 (95% CI 0.67 to 0.75). For LVEF <50%, the c-statistic increased from 0.66 (95% CI 0.60 to 0.72) to 0.76 (95% CI 0.70 to 0.81). For LVEF <45%, the c-statistic of the baseline model was already 0.80 (95% CI 0.72 to 0.87) and improved to 0.86 (95% CI 0.78 to 0.93). In the models predicting LVEF <54/52% and <50%, no survivor met the preset threshold probability of <1%. The results related to the models predicting LVEF <52/54% and LVEF <50% can be found in online supplemental file D. Only for model predicting LVEF <45% could a strong discriminatory ability be demonstrated with possible clinical value (figure 3).

For this latter model, the LASSO method selected five ECG abnormalities and two continuous measures (heart rate and QTc time). After adjusting for relevant patient and treatment-related characteristics, the binary variables left bundle branch block, left atrial enlargement, left heart axis and Cornell's criteria for LV hypertrophy remained independently associated with LVEF <45% (online supplemental file D, table 7). A new variable 'abnormal ECG based on LASSO analysis' was defined as the presence of any of these binary ECG abnormalities (see table 2). Also, increasing heart rate remained independently associated with LVEF <45%. Persistent supraventricular rhythm and increasing QTc time were not included in the final model because their association with LVEF <45% was non-significant. In the final logistic regression model, the OR of 'abnormal ECG based on LASSO analysis' was 7.2 (95% CI 3.0 to 18.0), and the OR for increased heart rate (in steps of 10) was 1.5 (95% CI 1.1 to 2.1). The Hosmer-Lemeshow calibration test yielded a p value of 0.1, indicating good calibration. Internal validation using bootstrapping yielded an optimism-corrected c-statistic of 0.83.

When applying a model-derived risk threshold of <1% to assume a low risk of LVEF <45%, the sensitivity of the model including 'abnormal ECG based on LASSO analysis' and heart rate was 93% (95% CI 76% to 99%), specificity was 56% (95% CI 52% to 59%), positive predictive value was 6% (95% CI 4% to 9%) and negative predictive value was 99.6% (95% CI 98% to 100%). Of the 478 survivors who had a predicted probability of <1%, 2 survivors had LVEF <45% (0.4%) (table 3). Adding 'abnormal ECG based on LASSO analysis' and heart rate to the model reclassified 49% (n=293) of survivors who were first designated as being at higher risk of LVEF <45% into true negatives. Online supplemental file D, table 8 demonstrates the diagnostic rule derived from the model including ECG.

DISCUSSION

Our study, in a nationwide cohort of ≥5-year childhood cancer survivors, aimed to investigate the role of ECG examination during cardiomyopathy surveillance. We demonstrated that the

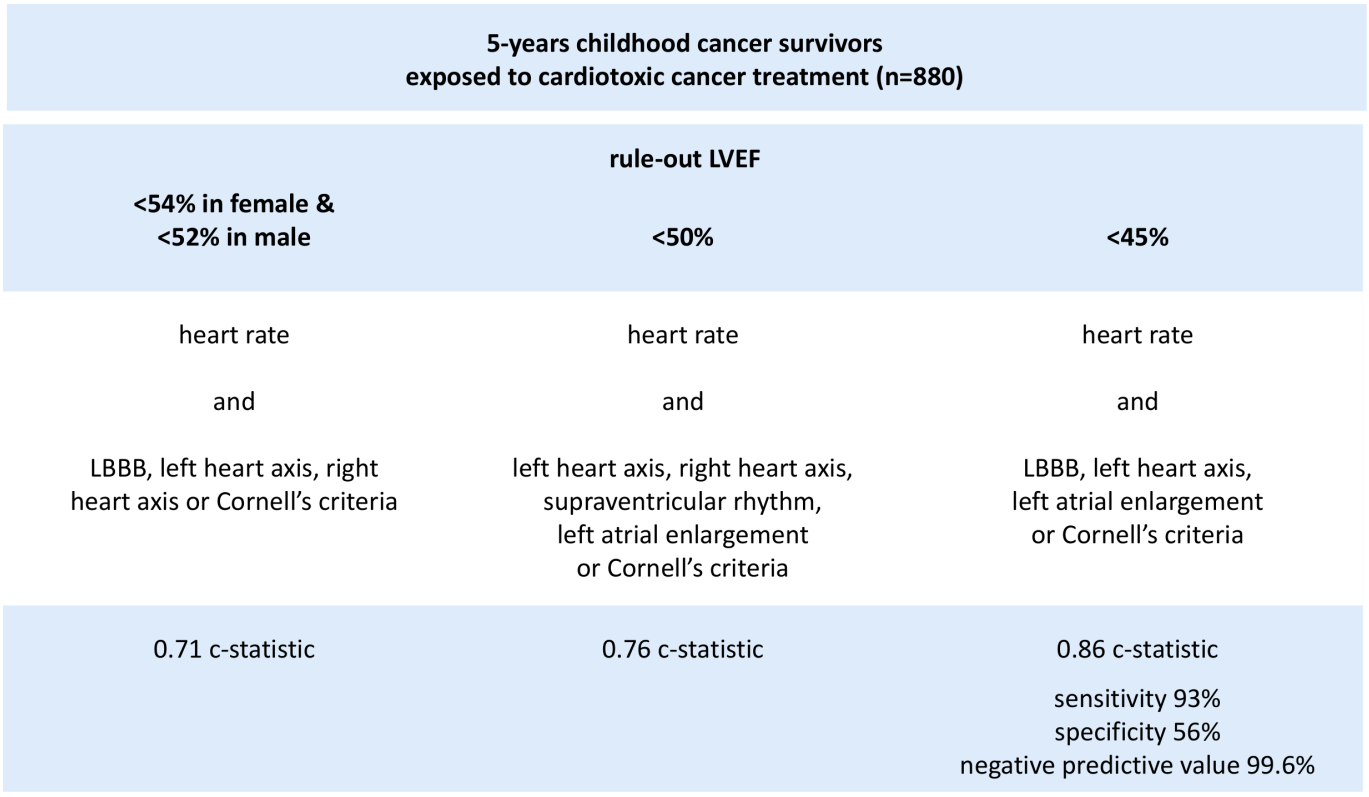

Figure 3 Comprehensive analysis of ECG data in logistic regression models predicting three categories of abnormal LVEF in childhood cancer survivors exposed to cardiotoxic cancer treatment. This figure illustrates the ECG data chosen through LASSO analysis and integrated into the binary variable 'abnormal ECG based on LASSO analysis' for each abnormal LVEF category. It also demonstrates the model's discriminative capacity, encompassing clinical variables such as sex, age at diagnosis, age at ECG, and dosage of anthracycline, mitoxantrone and radiotherapy, alongside the selected ECG data. The provided diagnostic metrics relate to ruling out LVEF <45%. LASSO, least absolute shrinkage and selection operator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

use of conventional ECG in at-risk survivors is inadequate to detect or exclude mild systolic dysfunction (LVEF <54/52%) and LVEF <50%, but may help to exclude therapeutically relevant systolic dysfunction (LVEF <45%). This can be done using relatively simple criteria from the ECG: complete left bundle branch block, left heart axis, left atrial dilatation, Cornell's criteria for LV hypertrophy and higher heart rate, without which a relevant LV dysfunction is highly unlikely. All these ECG abnormalities have been previously associated with decreased myocardial function in the general population.[9 19] Incorporating such a triage strategy into regular cardiomyopathy surveillance may help to reduce the number of echocardiograms with minimal risk of missing survivors with a therapeutically relevant LVEF.

Some of the results from the St Jude Lifetime Study in 2715 survivors were replicated, by showing that ECG abnormalities most often occurred in survivors exposed to heart RT.[24] We demonstrated that their rate is significantly higher compared with siblings for both major (24% vs 14%) and minor abnormalities (67% vs 50%) when adjusted for sex and age. We established that abnormalities suggestive for vascular events (Q waves and ST segment deviations) clearly contributed to these rates. Furthermore, the relatively high number of high R waves in the left precordial leads and left atrial dilatation on ECG could be related to the suggestion that survivors exposed to heart RT have an increased risk of concentric LV remodelling.[25]

An interesting aspect of our analysis is that ECG abnormalities associated with heart RT, such as Q waves and ST-T abnormalities, were not selected by LASSO for detection of LVEF <45%. However, those abnormalities might still relate to vascular or coronary events[8] and the method of detection would then be CT angiography. Studies in the general population established that a silent myocardial infarction detected by ECG is an independent risk factor for future heart failure.[26 27] Although we did not find an association of these specific ECG abnormalities with LV dysfunction, follow-up of survivors with these ischaemic findings may be warranted for other reasons such as preventive programmes focusing on vascular or ischaemic heart disease.

Our results indicate that the ECG abnormalities included in the model are more likely to follow increasing severities of cardiac dysfunction than that they are predecessors of it. This notion is supported by previous reports on increasing sensitivity of ECG abnormalities for more severe degrees of LV dysfunction.[11 12] However, it may be that more sensitive ECG markers will be found that can distinguish those with more moderate degrees of LV dysfunction from those with a normal LV function.

The goal of cardiomyopathy surveillance is to detect myocardial dysfunction before heart failure occurs. The main drawback of the strategy proposed in our study is the inability to detect survivors with an LVEF between 45% and 52/54%. Also, the current guideline does not yet include recommendations for adjusting the screening frequency for an LVEF between 45% and 52/54%, but only recommends follow-up based on the cardiotoxic cancer treatment dose.[2] The triage strategy for LVEF <45% proposed in our study is a first step and will probably be refined by blood biomarkers.

Future research, such as clinical utility analysis, may confirm or deny whether ECG patterns are useful for excluding survivors from echocardiography. Whether echocardiography, for example, can be deferred for 1 or 2 years remains unknown. Also, the association

Table 2 Multivariable logistic regression models predicting the presence of LVEF <45% in the cardiomyopathy surveillance group (n total=880*, n with the outcome=27)

	OR (95% CI)	P value	AIC value	AUC (95% CI)	H-L test
Model 1			227	0.80 (0.72 to 0.87)	0.7
Male sex (vs female)	1.3 (0.6 to 3.0)	0.5			
Age at cancer diagnosis, /5 years	0.7 (0.4 to 1.1)	0.1			
Age at follow-up, /10 years	*2.0 (1.2 to 3.5)*	*0.01*			
Cumulative anthracycline dose, /100 mg/m^2	*1.8 (1.4 to 2.3)*	*<0.001*			
Mitoxantrone dose, /10 mg/m^2	*1.4 (1.1 to 1.6)*	*<0.001*			
Heart RT dose, /10 Gray	1.1 (0.8 to 1.5)	0.5			
Model 2			202	0.86 (0.78 to 0.93)	0.1
Male sex (vs female)	1.5 (0.7 to 3.7)	0.3			
Age at cancer diagnosis, /5 years	0.7 (0.4 to 1.2)	0.3			
Age at follow-up, /10 years	1.4 (0.8 to 2.6)	0.2			
Cumulative anthracycline dose, /100 mg/m^2	*1.5 (1.2 to 2.0)*	*<0.001*			
Mitoxantrone dose, /10 mg/m^2	*1.4 (1.1 to 1.7)*	*<0.001*			
Heart RT dose, /10 Gray	1.02 (0.7 to 1.4)	0.9			
Abnormal ECG (vs normal)†	*7.2 (3.0 to 18.0)*	*<0.001*			
Heart rate, /10	*1.5 (1.1 to 2.1)*	*0.01*			

Cardiovascular risk factors were not included in models 1 and 2.
*We could not analyse n=143 survivors because data on the included variables and/or data on the outcome were missing.
†Abnormal ECG=presence of left bundle branch block, left atrial enlargement, left heart axis or Cornell's criteria.
AIC, Akaike information criterion; AUC, area under the curve; H-L, Hosmer and Lemeshow; LVEF, left ventricular ejection fraction; RT, radiotherapy.

between specific ECG abnormalities and future cardiac diseases[7–9] needs further exploration in survivors. Recent studies demonstrated that artificial intelligence may open new possibilities for ECG in predicting asymptomatic LV dysfunction with more subtle markers than used in our study.[28] Incorporating ECG abnormalities during follow-up could also refine the prediction of future LV dysfunction as has been demonstrated for LVEF results.[29]

Study limitations

Besides providing detailed information on ECG abnormalities in survivors at risk of cardiotoxicity, some limitations need to be considered. The disadvantage of a cross-sectional design is the different follow-up duration. We could not evaluate the presence or absence of major ECG abnormalities in all 1610 participants due to missing ECG examination (14%) or poor ECG lead quality (8%). After careful evaluation of the data, we considered this as missing at random and assumed a negligible effect on the results. Furthermore, we used FIJI software[30] which allows very precise measurements of the ECG with good or excellent interobserver agreement (interclass correlation coefficient 0.6–0.99). As a result, more ECG abnormalities such as Q waves may have been detected in survivors as well as in siblings. Given the small number of events in our analysis, thorough external validation of our results remains an important part of future research. Nevertheless, the prevalence of heart failure was still higher than in the younger general population.[23]

Table 3 Contingency table and diagnostic accuracy of the model including ECG when applying an estimated probability of <1% to assume a low risk of LVEF<45% in the cardiomyopathy surveillance group

	No. LVEF≥45%	No. LVEF<45%
No. Estimated probability<1%	476	2
No. Estimated probability≥1%	371	25
Sensitivity (95% CI)	93 (76–99)	
Specificity (95% CI)	56 (52–59)	
Positive predicted value (95% CI)	6 (4-9)	
Negative predicted value (95% CI)	99.6 (98-100)	

LVEF, left ventricular ejection fraction.

CONCLUSION

Specific ECG abnormalities are associated with worse myocardial function in survivors at risk of cardiomyopathy. Although ECG abnormalities may improve models for detecting moderate to severe LV dysfunction, the utility of a clinical model including ECG is currently limited to safely reduce echocardiographic testing in survivors at risk of cardiomyopathy.

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Supplementary file

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A. Additional information on cancer treatment variables

Protocol – data collection radiotherapy exposure involving the heart region

Radiotherapy exposure characterization

Based on the available information on the radiotherapy field(s) (location) from the letter of the pediatric radiation oncologist, each treatment was assigned to one or more body compartments, including head, neck, spine, thorax, abdominopelvic, upper- and lower extremities. Total body irradiation (TBI) was considered separately. Validation of radiotherapy data was performed by experts in radiotherapy.

We calculated the total maximum prescribed dose as the maximum dose to the smallest field, consisting of the sum of the full-field dose (primary) and the boost dose.

Furthermore, all our calculations include radiotherapy doses for both the primary tumor and any recurrences. If the same body part was re-irradiated the respective doses were summed to derive the maximum dose to the smallest field. In case the recurrence treatment was given as a non-overlapping field in the same body part (e.g. for primary tumor and recurrences or metastases both in the lungs for example), the dose to the field with the highest dose was assigned as body compartment dose for our study.

For the DCCSS LATER 2 CARD we focused on thorax, spine, abdominopelvic and TBI as they possibly involve the heart region. The specific fields exposing the body compartments spine and abdominopelvic are shown in the table below. In collaboration with MD Anderson Cancer Center, Houston, the United States and Gustave Roussy, Chevilly Larue, France, we estimated the mean dose received by the whole heart after total spine or abdominopelvic radiotherapy by using radiation dose reconstruction methods[1-6]. Based on a subset of 110 survivors, we derived percentages of dose received by the whole heart, by dividing the total prescribed dose and the estimated mean whole heart dose. As a result, we used 55% of the maximum prescribed spine dose and 10% of the maximum prescribed abdominopelvic dose to estimate the dose received by the whole heart. Furthermore, we used 100% of the maximum prescribed thorax dose to estimate the dose received by the whole heart. If more than one of above body compartments were irradiated, the highest dose was assigned as the dose received on the heart region. Finally, we added 100% of the total prescribed TBI dose to estimate the final radiotherapy dose on the heart region.

Uniform radiotherapy (RT) body compartment classification system

RT body compartments	Childhood cancer-specific treatment fields
Spine	Craniospinal
	Total spine
	Spine, thoracic region
	Spine, lumbar region
	Spine, sacral region
	Spine, not otherwise specified
Thorax	Thorax
	Mantle field
	Mantle field without mediastinal
	Scapula left
	Scapula right
	Scapula both sides
	Scapula, side unknown
	Ribs, sternum, clavicle
	Mediastinal
	Parasternal
	Axilla
	Supraclavicular
Abdominopelvic	Abdominal
	Liver
	Spleen
	Paraaortic field
	Paraaortic field plus spleen
	Inverted-Y field
	Inverted-Y field plus spleen
	Pelvis (including iliacal field)
	Parailliacal field
	Inguinal field

Definitions of ECG abnormalities according to the Minnesota Code

Major Abnormalities	**Minnesota Codes**
Major Q wave abnormalities	MC 1-1, 1-2
Minor Q wave abnormalities plus ST-T abnormalities	MC I-3 plus MC 4-1 or 4-2, or 5-1 or 5-2
Major Isolated ST-T abnormalities	MC 4-1 or 4-2 or 5-1 or 5-2
Complete or intermittent LBBB	MC 7-1
Complete or intermittent RBBB	MC 7-2
Nonspecific intraventricular block	MC 7-4
RBBB with left anterior hemiblock	MC 7.8
Brugada pattern	MC7-9
Left ventricular hypertrophy plus ST-T abnormalities	MC 3-1 plus MC 4-1 or 4-2 or 5-1 or 5-2
Major QT prolongation	QTI ≥ 116%
Atrial Fibrillation or Flutter (Continuous or intermittent)	MC 8-3
Third-degree AV block	MC 6-1
Second-degree AV block	MC 6-2
Ventricular preexcitation pattern	MC 6-4
Artificial pacemaker	MC 6-8
Ventricular fibrillation or ventricular asystole	MC 8-2
Supraventricular tachycardia (SVT)	MC 8-4-2 or MC 8-4-1with HR>140

Minor Abnormalities	**Minnesota Codes**
Minor Isolated Q/QS waves	MC 1-3
Minor ST/T abnormalities	MC 4-3, 4-4, 5-3, 5-4
High R waves (left ventricular)	MC 3-1, 3-3, 3-4
High R waves (right ventricular)	MC 3-2
ST segment elevation	MC 9-2
Incomplete RBBB	MC 7-3
Incomplete LBBB	MC 7-6, 7-7
Minor QT prolongation	QTI ≥ 112%
Short PR interval	MC 6-5
Long PR interval	MC 6-3
Left axis deviation	MC 2-1
Right axis deviation	MC 2-2
Premature beats (supraventricular)	MC 8-1-1
Premature beats (ventricular)	MC 8-1-2
Premature beats (combined)	MC 8-1-3, 8-1-5
Wandering atrial pacemaker	MC 8-1-4
Sinus tachycardia	MC 8-7
Sinus bradycardia	MC 8-8
Supraventricular rhythm persistent	MC 8-4-1
Low QRS voltage	MC 9-1
High amplitude P wave	MC 9-3
Left atrial enlargement	MC 9-6

Prineas RJ, Crow RS, Zhang Z: The Minnesota code manual of electrocardiographic findings, 2009

B. Characteristics of the participating and non-participating survivors from the DCCSS LATER 2 CARD study

	Participant n=1,608	Non-participants[a] n=1,383
Sex (%)		
Female	48	39
Year of diagnosis (%)		
<1970	1	1
1970-1979	12	11
1980-1989	30	30
1990-1999	45	48
≥2000	12	10
Age at diagnosis (%)		
<5 years	43	42
5-9 years	29	28
10-14 years	22	23
15-17 years	6	7
Age at invitation (%)		
<18 years	2	1[b]
18-29 years	33	33[b]
30-39 years	37	40[b]
≥40 years	29	26[b]
Time since cancer diagnosis (%)		
10-19 years	22	21
20-29 years	41	44
30-39 years	29	28
40-49 years	8	7
50-59 years	1	0
Type of cancer diagnosis (%)		
Leukemia	42	43
Lymphoma	23	25
CNS	3	5
Neuroblastoma	3	3
Renal tumors	12	9
Hepatic tumors	1	2
Bone tumors	8	8
Soft tissue sarcomas	5	5
Germ cell tumors	2	2

[a] Includes the refusers (someone who actively said no) and the non-responders (someone who did not respond to the study invitation and thus did not actively say no).
[b] age at invitation was not available for refusers.

C. Comparison of the prevalence of the separate major, minor and other ECG abnormalities between survivors (all and per cardiotoxic cancer exposure) and siblings

	Siblings	**Survivors**				
		All	Potentially cardiotoxic therapy	Only anthracyclines or mitoxantrone	Only heart RT	Both anthracyclines/ mitoxantrone and heart RT
	n=272	n=1,381[*]	n=155	n=809	n=158	n=255
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Presence of any major abnormality	34/251 (14)	199/1,249 (16)	17/138 (12)	105/732 (14)	34/142 (24)[a,b]	42/233 (18)
Major Q wave abnormality	11/254 (4)	76/1,264 (6)	7/143 (5)	37/740 (5)	17/145 (12)[a]	15/232 (7)
Major isolated ST-T abnormality	16/258 (6)	70/1,277 (6)	4/145 (3)	43/745 (6)	11/146 (8)	11/237 (5)
Minor Q wave abnormalities *plus* ST-T abnormality	2/230[1] (1)	7/1,184[1] (1)	1/136 [1] (0.7)	4/695[1] (0.6)	1/133[1] (0.8)	1/217[1] (0.5)
Left ventricular hypertrophy *plus* ST-T abnormalities	3/262 (1)	11/1,297 (1)	1/146 (0.7)	6/764 (0.8)	1/148 (0.7)	3/235 (1)
Major QT prolongation	2/265 (1)	6/1,339 (0.5)	2/147 (1)	1/787 (0.1)	2/153 (1)	1/248 (0.4)
Complete left bundle branch block	0/264 (0)	21/1,314 (2)[a]	2/145 (1)	9/774 (1)	2/149 (1)	8/242 (3)[a]
Complete right bundle branch block	2/263 (1)	9/1,309 (1)	1/144 (0.7)	5/770 (0.6)	0/149 (0)	3/242 (1)
Other intraventricular block	2/262 (1)	15/1,309 (1)	2/144 (1)	7/770 (0.9)	2/149 (1)	4/242 (2)
Bifascicular block	0/263 (0)	2/1,310 (0.2)	1/144 (0.7)	1/770 (0.1)	0/149 (0)	0/242 (0)
WPW pattern	0/272 (0)	2/1,381 (0.1)	0/155 (0)	0/809 (0)	1/158 (0.6)	1/255 (0.4)
Pacemaker	0/272 (0)	7/1,381 (1)	0/155 (0)	5/809 (0.6)	0/158 (0)	2/255 (0.8)
Presence of any minor abnormality	131/263 (50)	750/1,320 (57)[a]	87/150 (58)	413/769 (54)	102/153 (67)[a,b]	145/242 (60)[a]
Minor Q-wave abnormality	12/251 (5)	91/1,262 (7)	11/142 (8)	54/742 (7)	12/144 (8)	14/229 (6)
Minor ST-T abnormality	14/256 (6)	131/1,283 (10)[a]	12/146 (8)	63/746 (8)[b]	20/150 (13)[a]	35/236 (15)[a,b]
High amplitude R waves right	3/260 (1)	6/1,324 (0.5)	1/153 (1)	2/771 (0.3)	3/152 (2)	0/242 (0)
High amplitude R waves left	19/254 (8)	170/1,279 (13)[a,b]	12/145 (8)	91/747 (11)[a]	28/148 (19)[a,b]	39/234 (17)[a,b]
Left atrial dilatation	15/272 (6)	194/1,379 (11)[a,b]	20/154 (13)[a,b]	96/809 (12)[a,b]	36/158 (23)[a,b]	40/252 (16)[a,b]
ST segment elevation	13/256 (5)	79/1,282 (6)	8/145 (6)	41/752 (6)	13/147 (9)	17/232 (7)
Incomplete right bundle branch block	21/260 (8)	109/1,298 (8)	8/144 (6)	63/763 (8)	15/148 (10)	23/238 (10)
Incomplete left bundle branch block	4/258 (2)	9/1,293 (1)	1/144 (1)	4/763 (1)	1/147 (1)	3/235 (1)
Minor QT prolongation	3/268 (1)	23/1,360 (2)	4/150 (3)	7/799 (1)	3/156 (2)	9/249 (4)[b]
Short PR interval	13/272 (5)	83/1,1381 (6)	8/155 (5)	49/809 (6)	10/158 (6)	15/253 (6)
Long PR interval	2/272 (1)	9/1,380 (1)	1/154 (1)	5/809 (1)	2/158 (1)	1/253 (0.4)
Left heart axis	6/265 (2)	39/1,326 (3)	2/146 (1)	25/781 (3)	3/150 (2)	9/244 (4)
Right heart axis	14/265 (5)	54/1,326 (4)	14/146 (10)	22/781 (3)[b]	8/150 (5)	10/244 (4)
Atrial or junctional premature beats	7/271 (3)	21/1,278 (2)	3/154 (2)	13/807 (2)	2/158 (1)	3/253 (1)

Ventricular premature beats	2/271 (1)	4/1,379 (0.3)	0/155 (0)	2/807 (0.2)	0/158 (0)	2/253 (0)
Sinus tachycardia	1/272 (0.4)	20/1,381 (1)	1/155 (1)	6/809 (1)	4/158 (3)	9/253 (4)[a,b]
Sinus bradycardia	30/272 (11)	69/1,381 (5)[a,b]	7/155 (5)[b]	57/809 (7)[a,b]	3/158 (2)[a,b]	2/253 (1)[a,b]
Supraventricular rhythm persistent	2/272 (1)	8/1,381 (1)	0/155 (0)	7/809 (1)	1/158 (1)	0/253 (0)
Low QRS amplitude	2/251 (1)	4/1,258 (0.3)	0/143 (0)	4/739 (1)	0/144 (0)	0/228 (0)
Other ECG patterns						
Cornell's Criteria	2/272 (0.7)	63/1,379 (5)[a]	3/155 (2)	32/808 (4)[a]	10/158 (6)[a]	18/254 (7)[a]
Beats per minute; median, IQR	60 (55-67)	65 (58-74)[a,b]	61 (56-69)[b]	63 (56-71)[a,b]	71 (62-81)[b]	70 (61-79)[a,b]
QRS duration (ms); median, IQR	92 (88-100)	92 (84-100)[a,b]	92 (88-100)	92 (84-100)[b]	92 (82-100)[b]	88 (80-100)[a,b]
QTc duration (ms); median, IQR						
Male	370 (355-389)	381 (362-398)[a,b]	379 (367-399)[a,b]	380 (362-397)[a,b]	383 (361-398)[a]	382 (361-405)[a,b]
Female	391 (376-408)	394 (377-412)[b]	393 (378-415)[b]	393 (376-410)[d]	397 (377-413)	398 (382-417)[a,b]

Abnormalities are not mutually exclusive; participants may have had more than 1 abnormality.
Prevalence was 0 in all treatment groups: Brugada pattern, atrial fibrillation, atrioventricular conduction defect, ventricular fibrillation or asystole and supraventricular tachycardia (missing in ~2%).
[1] missing in >10%.
*in 4 survivors the cardiotoxic cancer treatment was unclear due to missing information on heart RT.
[a] unadjusted comparison with siblings demonstrated a p-value <0.05.
[b]after adjustment for sex and age at ECG, being a survivor (versus sibling) is significantly associated with the outcome.

ECG=electrocardiographic, IQR=interquartile range, n=number of participants with the events, N=total number of participants evaluated, RT=radiotherapy, WPW= Wolff-Parkinson-White

Table 1. Comparison of the prevalence of the separate major and minor ECG abnormalities between survivors

D. Association between ECG and systolic function – additional results

Full list of variables included in the LASSO models:

- Code 1.1
- Code 1.2
- Code 1.3
- Code 2.1
- Code 2.2
- Code 3.1
- Code 3.2
- High R waves - left ventricular (Code 3.1, Code 3.3, Code 3.4)
- Code 4.1
- Code 4.2
- Code 4.3
- Code 4.4
- Code 5.2
- Code 5.3
- Code 5.4
- Code 6.3
- Code 6.5
- Code 7.1.1
- Code 7.2.1
- Code 7.3
- Code 7.4
- Incomplete left bundle branch block (Code 7.6, Code 7.7)
- Code 7.8
- Code 8.1.1
- Code 8.1.2
- Code 8.4.1
- Code 8.7
- Code 8.8
- Code 9.1
- Code 9.2
- Code 9.6
- Major QT prolongation (QTI ≥ 116%)
- Minor QT prolongation (QTI ≥ 112%)
- Cornell's criteria
- Frequency (continuous variable)
- QTd interval (continuous variable)
- QRS interval (continuous variable)
- QTc interval (continuous variable)
- PQ interval (continuous variable)

with a normal LVEF and an abnormal LVEF

	Normal LVEF*	Abnormal LVEF	
n/N (%)		≥45%	<45%
Presence of any major abnormality	85/643 (13)	30/174 (17)	11/28 (39)[a,b]
Major Q wave abnormality	36/648 (6)	10/117 (6)	4/28 (14)
Major isolated ST-T abnormality	36/655 (6)	12/177 (7)	2/ (7)
Minor Q wave abnormalities *plus* ST-T abnormality	3/611 (1)	1/163 (1)	0/24 (0)
Left ventricular hypertrophy *plus* ST-T abnormalities	5/667 (1)	1//180 (1)	1/27 (4)
Major QT prolongation	3/695 (0.4)	0/184 (0)	0/28 (0)
Complete left bundle branch block	3/681 (0.4)	3/181 (2)	4/27 (15)[a,b]
Complete right bundle branch block	3/679 (0.4)	3/181 (7)	0/27 (0)
Other intraventricular block	7/679 (1)	1/181 (1)	2/27 (7)[a,b]
Bifascicular block	1/679 (0.1)	0/181 (0)	0/27 (0)
Presence of any minor abnormality	369/681 (54)	114/184 (62)[b]	20/27 (74)[a]
Minor Q-wave abnormality	49/653 (8)	17/177 (10)	4/27 (15)
Minor Isolated Q wave abnormality	41/648 (6)	16/177 (9)	4/27 (15)
Minor ST-T abnormality	58/658 (9)	22/179 (12)	7/27 (26)[a,b]
High amplitude R waves right	3/680 (0.4)	2/181 (1)	0/28 (0)
High amplitude R waves left	93/657 (14)	28/179 (16)	5/27 (19)
Left atrial dilatation	82/717 (11)	32/188 (17)[a]	11/28 (39)[a,b]
ST segment elevation	43/658 (7)	12/178 (7)	0/27 (0)
Incomplete right bundle branch block	59/671 (9)	20/181 (11)	1/27 (4)
Incomplete left bundle branch block	3/668 (0.4)	1/179 (1)	0/27 (0)
Minor QT prolongation	10/707 (1)	4/186 (2)	1/28 (4)
Short PR interval	40/718 (6)	17/188 (9)	1/28 (4)
Long PR interval	6/718 (1)	0/188 (0)	0/28 (0)
Left heart axis	15/691 (2)	7/183 (4)	4/27 (15)[a,b]
Right heart axis	19/691 (3)	11/183 (6)[a,b]	0/27 (0)
Atrial or junctional premature beats	13/718 (2)	2/188 (1)	0/28 (0)
Ventricular premature beats	1/718 (0.1)	0/188 (0)	0/28 (0)
Sinus tachycardia	7/718 (1)	4/188 (2)	2/28 (7)[a,b]
Sinus bradycardia	44/718 (6)	5/188 (3)	0/28 (0)
Supraventricular rhythm persistent	4/718 (1)	1/188 (1)	1/28 (4)
Low QRS amplitude	1/646 (0.2)	1/176 (1)	0/27 (0)
Other ECG measures			
Cornell's criteria	10/718 (1)	4/188 (2)	5/28 (18)[a,b]
Heart rate; median, IQR	63 (57-72)	69 (60-80)[a,b]	73 (61-83)[a,b]
QRS duration (ms); median, IQR	92 (84-100)	88 (84-100)	100 (89-123)[a,b]
QRS duration >100 ms	106/718 (15)	31/81 (17)	13/28 (46)[a,b]
QTc duration (ms); median, IQR			
Male	379 (361-397)	377 (358-402)	388 (382-441)[a,b]
Female	390 (374-409)	396 (380-415)	412 (400-438)[a,b]

* LVEF≥54% in female, LVEF≥52% in male

[a] Fisher's exact test demonstrated a p-value <0.05

[b] comparison with normal LVEF, adjusted for sex and age at ECG, demonstrated a p-value <0.05

ECG=electrocardiographic, IQR=interquartile range, n=number of participants with the events, N=total number of participants evaluated, LVEF=left ventricular dysfunction, RT=radiotherapy

Table 2. Characteristics of the analyzed survivors in the cardiomyopathy surveillance group

	n=880
Demographics, diagnosis and treatment history	
Sex, n (%)	
Female	394 (45%)
Age at diagnosis, years, median [IQR]	*6.3 [3.2-11.4]*
0-<5	361 (41)
5-<10	253 (29)
10-<15	209 (24)
15-18	57 (6)
Primary cancer diagnosis, n (%)	
Leukemias	351 (40)
Lymphomas/reticuloendothelial	227 (26)
CNS, intracranial and intraspinal neoplasms	29 (3)
Neuroblastoma and other peripheral nervous cell tumors	26 (3)
Renal tumors	107 (12)
Hepatic tumors	8 (1)
Bone tumors	72 (8)
Soft tissue and other extraosseous sarcomas	49 (6)
Germ cell tumors	9 (1)
Others	2 (0.2)
Age at follow-up, years, median [IQR]	*34.3 [28.5-42.6]*
15-<25, n (%)	111 (13)
25-<35	352 (40)
35-<45	274 (31)
≥45	143 (16)
Time since cancer diagnosis, years, median [IQR]	*26.6 [21.7-33.3]*
10-<20, n (%)	264 (19)
20-<30	580 (42)
30-<40	402 (29)
≥40	135 (10)
Cumulative anthracycline dose, mg/m^2, median [IQR]	*180 [120-275]*
No anthracyclines, n (%)	126 (14)
1-100	127 (14)
100.1-250	424 (48)
>250	203 (23)
Mitoxantrone dose, mg/m^2 , median [IQR]	*40 [20-72]*
No mitoxantrone, n (%)	825 (94)
1-40	35 (4)
>40	20 (2)
RT including the heart region dose, Gy, median [IQR]	*12 [3.5-20.3]*
No RT including the heart region, n (%)	592 (67)
1-15	186 (21)
15.1-30	60 (7)
>30	42 (5)
Outpatient clinic data,	
LVEF<45% at evaluation, n (%)	27 (3)

IQR=interquartile range, LVEF= left ventricular ejection fraction, n=number, RT = radiotherapy, y=year.

Table 3. Multivariable models predicting the presence of LVEF <52% in males/ <54% in females in the cardiomyopathy surveillance group (n total = 880[a], n with the outcome = 203)

n=880	OR (95%CI)	p-value	AIC value	AUC (95%CI)	H-L test
Model 1			924	0.66 (0.61-0.70)	0.7
Male sex (versus female)	*0.6 (0.4-0.8)*	*0.001*			
Age at cancer diagnosis, /5 years	*0.7 (0.6-0.8)*	*0.003*			
Age at follow-up, /10 years	1.2 (0.9-1.4)	0.2			
Cumulative anthracycline dose, /100 mg/m2	*1.3 (1.2-1.4)*	*<0.001*			
Mitoxantrone dose, /10 mg/m2	1.0 (0.9-1.1)	0.9			
Heart RT dose, /10 Gray	*1.3 (1.1-1.5)*	*<0.001*			
Model 2			891	0.71 (0.67-0.75)	0.09
Male sex (versus female)	*0.5 (0.4-0.8)*	*<0.001*			
Age at cancer diagnosis, /5 years	*0.8 (0.6-0.9)*	*0.01*			
Age at follow-up, /10 years	1.0 (0.8-1.3)	0.7			
Cumulative anthracycline dose, /100 mg/m2	*1.3 (1.2-1.5)*	*<0.001*			
Mitoxantrone dose, /10 mg/m2	1.0 (0.9-1.1)	0.9			
Heart RT dose, /10 Gray	*1.2 (1.01-1.4)*	*0.03*			
Abnormal ECG (versus normal)[b]	*3.0 (1.8-5.0)*	*<0.001*			
Heart rate, per 10	*1.4 (1.2-1.5)*	*<0.001*			

[a] We could not analyse n=148 survivors because data on the included variables and/or data on the outcome were missing.
[b] Abnormal ECG = presence of left bundle branch block, left heart axis, right heart axis or Cornell's criteria.
AIC=Akaike information criterion, CI=confidence interval, ECG=electrocardiography, LEVF = left ventricular ejection fraction, OR = odds ratio

Table 4. Multivariable model including all the ECG variables selected by LASSO predicting the presence of LVEF <52% in males/<54% in females in the cardiomyopathy surveillance group (n total = 880[a], n with the outcome = 203)

n=880	OR (95%CI)[b]	p-value
Left bundle branch block (versus no)	*4.5 (1.1-22.1)*	*0.04*
Left atrial enlargement (versus no)	1.3 (0.8-2.1)	0.2
Short PR interval	1.6 (0.8-2.9)	0.2
Left heart axis (versus no)	*2.6 (1.01-6.2)*	*0.04*
Right heart axis (versus no)	*2.3 (0.97-5.0)*	*0.05*
Cornell's criteria (versus no)	*3.2 (1.1-9.1)*	*0.03*
Heart rate, per 10	*1.3 (1.2-1.5)*	*<0.001*
QTd time. per 10 ms	1.04 (0.97-1.1)	0.2

[a] We could not analyse n=148 survivors because data on the included variables and/or data on the outcome were missing.
[b] Adjusted for sex, age at diagnosis, age at ECG and dose of anthracycline, mitoxantrone and heart RT.
ECG=electrocardiographic, CI=confidence interval, LVEF=left ventricular dysfunction, OR= odds ratio, RT=radiotherapy

Table 5. Multivariable models predicting the presence of LVEF<50% in the cardiomyopathy surveillance group (n total = 880[a], n with the outcome = 94)

n=880	OR (95%CI)	p-value	AIC value	AUC (95%CI)	H-L test
Model 1			581	0.66 (0.60-0.72)	0.4
Male sex (versus female)	1.2 (0.001-0.07)	0.4			
Age at cancer diagnosis, /5 years	*0.7 (0.5-0.95)*	*0.02*			
Age at follow-up, /10 years	1.3 (0.98-1.8)	0.07			
Cumulative anthracycline dose, /100 mg/m2	*1.4 (1.2-1.7)*	*<0.001*			
Mitoxantrone dose, /10 mg/m2	1.1 (0.9-1.2)	0.5			
Heart RT dose, /10 Gray	*1.3 (1.1-1.6)*	*0.005*			
Model 2			539	0.76 (0.70-0.81)	0.2
Male sex (versus female)	1.2 (0.7-1.8)	0.5			
Age at cancer diagnosis, /5 years	0.8 (0.6-1.02)	0.07			
Age at follow-up, /10 years	1.1 (0.8-1.5)	0.6			
Cumulative anthracycline dose, /100 mg/m2	*1.4 (1.2-1.6)*	*<0.001*			
Mitoxantrone dose, /10 mg/m2	1.1 (0.9-1.2)	0.5			
Heart RT dose, /10 Gray	1.2 (0.97-1.5)	0.08			
Abnormal ECG (versus normal)[b]	*3.8 (2.4-6.1)*	*<0.001*			
Heart rate, per 10	*1.4 (1.2-1.6)*	*<0.001*			

[a] We could not analyse n=148 survivors because data on the included variables and/or data on the outcome were missing.
[b] Abnormal ECG = presence of left atrial enlargement, left heart axis, right heart axis, supraventricular rhyhm or Cornell's criteria.
AIC=Akaike information criterion, CI=confidence interval, ECG=electrocardiography, LEVF = left ventricular ejection fraction, OR = odds ratio

Table 6. Multivariable model including all the ECG variables selected by LASSO predicting the presence of LVEF <50% in the cardiomyopathy surveillance group (n total = 880[a], n with the outcome =94)

n=880	OR (95%CI)[b]	p-value
Left bundle branch block (versus no)	2.9 (0.6-14.6)	0.2
Left atrial enlargement (versus no)	*2.4 (1.3-4.2)*	*0.003*
Left heart axis (versus no)	*4.2 (1.4-11.3)*	*0.007*
Right heart axis (versus no)	*4.1 (1.5-10.2)*	*0.003*
Q-waves Code 1.2	1.7 (0.7-4.0)	0.3
Sinus tachycardia	1.7 (0.4-7.4)	0.5
Supraventricular rhythm persistent CODE8.4.1	*8.4 (1.1-48.7)*	*0.02*
Cornell's criteria (versus no)	*3.5 (1.1-10.8)*	*0.03*
Heart rate, per 10	1.4 (1.1-1.7)	0.002
QRS max	1.2 (097-1.4)	0.1

[a] We could not analyse n=148 survivors because data on the included variables and/or data on the outcome were missing.
[b] Adjusted for sex, age at diagnosis, age at ECG and dose of anthracycline, mitoxantrone and heart RT.
ECG=electrocardiographic, CI=confidence interval, LVEF=left ventricular dysfunction, OR= odds ratio, RT=radiotherapy

Table 7. Multivariable model including all the ECG variables selected by LASSO predicting the presence of LVEF<45% in the cardiomyopathy surveillance group (n total = 880[a], n with the outcome = 27)

n=874	OR (95%CI)[b]	p-value
Left bundle branch block (versus no)	*11.1 (1.9-60.5)*	*0.01*
Left atrial enlargement (versus no)	*3.0 (1.1-7.9)*	*0.03*
Left heart axis (versus no)	*5.1 (1.03-2.1)*	*0.03*
Supraventricular rhythm persistent (versus no)	11.6 (0.4-125)	0.08
Cornell's criteria (versus no)	*7.7 (1.7-33.5)*	*0.01*
Heart rate, per 10	*1.5 (1.01-2.1)*	*0.04*
QTc time. per 100 ms	1.09 (0.9-1.3)	0.3

[a] We could not analyse n=148 survivors because data on the included variables and/or data on the outcome were missing.
[b] Adjusted for sex, age at diagnosis, age at ECG and dose of anthracycline, mitoxantrone and heart RT.
ECG=electrocardiographic, CI=confidence interval, LVEF=left ventricular dysfunction, OR= odds ratio, RT=radiotherapy

Table 8. Diagnostic rule derived from model 2 Table 3.

Sex	**Points**
Female	0
Male	8
Age at cancer diagnosis (in years)	**Points**
0	20
8	11
16	2
18	0
Age at ECG (in years)	**Points**
15	0
30	10
60	31
70	37
Cumulative anthracycline dose (in mg/m2)	**Points**
0	0
100	8
300	24
500	40
700	55
800	63
Mitoxantrone dose (in mg/m2)	**Points**
0	0
40	25
80	50
120	75
160	100
Heart RT (in Gray)	**Points**
0	0
15	1
40	2
60	3
ECG	
Normal	0
Abnormal	36
Heart rate	
40	0
60	16
80	31
100	47
120	63
130	71
Total score	

Total score	**Probability of LVEF<45% estimated by the rule**

0-69	<1%
70-99	1-<5%
100-113	5-<10%
114-128	10-<20%
129-153	20-<50%

ECG=electrocardiography, LVEF=left ventricular dysfunction.

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