

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 methods¹⁻⁶. 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 \geq 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 8-4-1 with 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 \geq 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			
	n=272 n/N (%)	All	Potentially cardiotoxic therapy	Only anthracyclines or mitoxantrone	Only heart RT	Both anthracyclines/ mitoxantrone and heart RT
		n=1,381* n/N (%)	n=155 n/N (%)	n=809 n/N (%)	n=158 n/N (%)	n=255 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 <i>plus</i> 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 <i>plus</i> 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)
<u>Other ECG patterns</u>						
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 ($QTI \geq 116\%$)
- Minor QT prolongation ($QTI \geq 112\%$)
- 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

n/N (%)	Normal LVEF*	Abnormal LVEF	
		≥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 <i>plus</i> ST-T abnormality	3/611 (1)	1/163 (1)	0/24 (0)
Left ventricular hypertrophy <i>plus</i> 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 extrasosseous 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/m ²	1.3 (1.2-1.4)	<0.001			
Mitoxantrone dose, /10 mg/m ²	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/m ²	1.3 (1.2-1.5)	<0.001			
Mitoxantrone dose, /10 mg/m ²	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, LVEF = 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/m ²	1.4 (1.2-1.7)	<0.001			
Mitoxantrone dose, /10 mg/m ²	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/m ²	1.4 (1.2-1.6)	<0.001			
Mitoxantrone dose, /10 mg/m ²	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 rhythm or Cornell's criteria. AIC=Akaike information criterion, CI=confidence interval, ECG=electrocardiography, LVEF = 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 (0.97-1.4)	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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