Diagnostic tools for early detection of cardiac dysfunction in childhood cancer survivors: Methodological aspects of the Dutch late effects after childhood cancer (LATER) cardiology study

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Background Cancer therapy-related cardiac dysfunction and heart failure are major problems in long-term childhood cancer survivors (CCS). We hypothesize that assessment of more sensitive echo- and electrocardiographic measurements, and/or biomarkers will allow for improved recognition of patients with cardiac dysfunction before heart failure develops, and may also identify patients at lower risk for heart failure.

Objective To describe the methodology of the Dutch LATER cardiology study (LATER CARD).

Methods The LATER CARD study is a cross-sectional study in long-term CCS treated with (potentially) cardiotoxic cancer therapies and sibling controls. We will evaluate 1) the prevalence and associated (treatment related) risk factors of subclinical cardiac dysfunction in CCS compared to sibling controls and 2) the diagnostic value of echocardiography including myocardial strain and diastolic function parameters, blood biomarkers for cardiomyocyte apoptosis, oxidative stress, cardiac remodeling and inflammation and ECG or combinations of them in the surveillance for cancer therapy-related cardiac dysfunction. From 2017 to 2020 we expect to include 1900 CCS and 500 siblings.

Conclusions The LATER CARD study will provide knowledge on different surveillance modalities for detection of cardiac dysfunction in long-term CCS at risk for heart failure. The results of the study will enable us to improve long-term follow-up surveillance guidelines for CCS at risk for heart failure. (Am Heart J 2020;219:89-98.)

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Netherlands Trial Registry (NTR) number 7481.

Funding: Dutch Heart Foundation Grant [CVON2015–21]. Kika/ODAS Grant 171 'DCOG LATER program'.

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Submitted December 28, 2018; accepted October 21, 2019.

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0002-8703

https://doi.org/10.1016/j.ahj.2019.10.010

The long-term survival of childhood cancer has increased considerably over the last few decades. With a 5-year overall survival of more than 80%,[1] the majority of childhood cancer patients nowadays will become long-term survivors. Unfortunately, the improved survival is accompanied by the occurrence of late adverse effects of treatment.[2,3] The cardiotoxic side effects of certain cancer treatments such as anthracyclines and chest directed radiotherapy are well-known and include heart failure, arrhythmias, coronary artery disease, valvular abnormalities and pericardial disease.[4]

Of these cardiotoxic side effects, cancer therapy-related heart failure in childhood cancer survivors (CCS) is the most frequently encountered problem: almost 5% of all CCS develops clinical heart failure within 40 years after childhood cancer diagnosis.[5] Moreover, mortality due to heart failure is six-fold higher in long-term CCS as compared to the general population and treatment related cardiac death is the leading cause of death after malignancies.[6,7]

Before clinical heart failure, a larger proportion of long-term CCS have a subclinical decline in left ventricular (LV) systolic function. The prevalence of subclinical LV systolic dysfunction varies in the literature, and is about 30% in different follow up periods when defined as a two-dimensional ejection fraction (EF) <50% or fractional shortening (FS) <30%.[3,8] In a recent study, prevalence of LV dysfunction was only 5.8% after a median follow up of 23 years but in that study LV systolic dysfunction was defined with more constraint as a three-dimensional EF <50%.[9] The Dutch surveillance guideline for long-term CCS defines cancer therapy-related cardiac dysfunction as a FS <30% or EF< 50%.[10]

Established treatment related risk factors for heart failure and subclinical LV systolic dysfunction in CCS are higher cumulative anthracycline doses (in a non-linear fashion with no safe dose threshold), higher cumulative mitoxantrone dose and chest directed radiotherapy (especially in combination with anthracyclines).[2,3,11] The type of anthracycline analogue and anthracycline infusion duration might also play a role.[12-16]

Surveillance for subclinical cardiac dysfunction may prevent further deterioration of LV function by timely initiating heart failure therapies.[17,18]

Currently, EF measured by two-dimensional echocardiography is the main parameter used in the surveillance for cancer therapy-related cardiac dysfunction and for clinical decision making in CCS.[16,19] However, the usefulness of EF is limited by a large variability of 10%.[20]

In the general population myocardial strain imaging emerges as a valuable tool to detect subclinical LV dysfunction that is superior in predicting heart failure and all-cause mortality compared to two-dimensional EF.[21-23] The prevalence of global longitudinal strain abnormalities in CCS with a preserved three-dimensional ejection fraction was 28% in a cohort study in 1820 CCS at a median of 23 years after cancer diagnosis.[9]

Another echocardiographic tool next to LV systolic dysfunction determined by 2D echocardiography is LV diastolic dysfunction which is encountered in 9–21% of long-term CCS, with severe dysfunctions mainly after (additional) chest directed radiotherapy.[8,9,24] Also diastolic dysfunction is a predictor of future heart failure in the general population.[25,26]

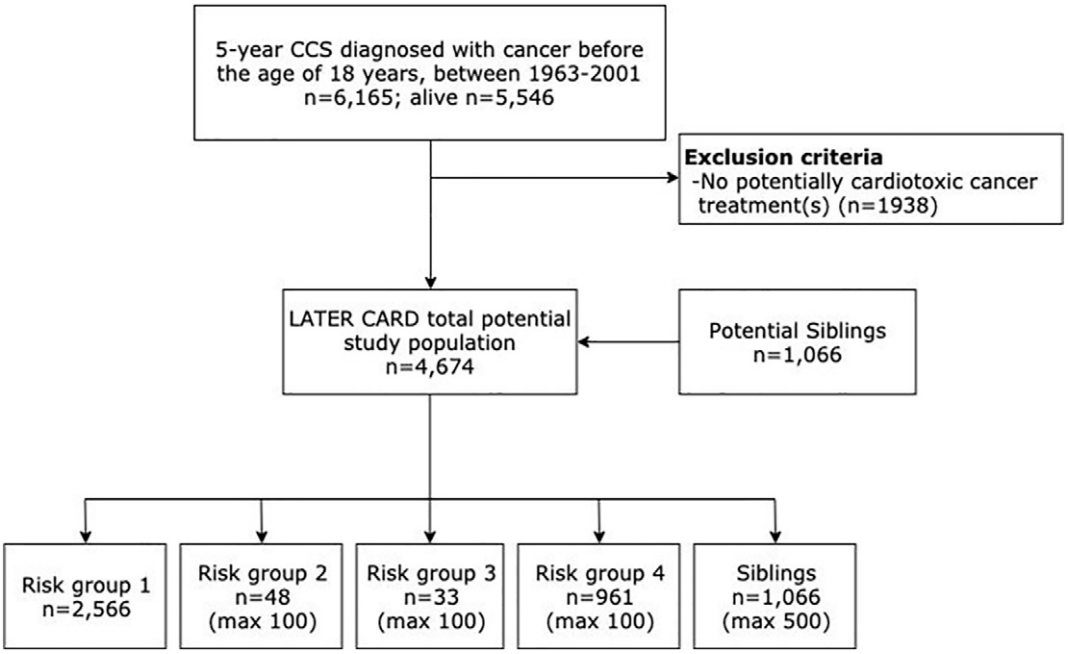
Studies have been performed that identified blood biomarkers that can detect subclinical cancer-treatment related cardiac dysfunction.[16] However, blood biomarkers are not yet recommended in the surveillance for cardiac dysfunction in long-term CCS.[10,16] Recently, we reviewed the literature on blood biomarkers for the diagnosis of LV dysfunction in long-term CCS and showed that NT-proBNP and troponins have a limited diagnostic value, which underlines the need to find more accurate biomarkers.[27]

The ability of ECG parameters to early detect cancer therapy-related cardiac dysfunction in CCS remains unknown.[16,28] Several studies in long-term CCS describe a high incidence and variety of electrocardiographic abnormalities.[29] Major ECG abnormalities were predictive for cardiac and all-cause mortality in a large CCS cohort but were not compared with echocardiographic abnormalities.[30] In a smaller long-term CCS cohort ECG abnormalities (mainly conduction disorders, high amplitude R waves and sinus bradycardia) were not predictive for echocardiographic abnormalities.[28] However, only one of these 340 CCS had evidence of systolic LV dysfunction with an EF< 50% and strain parameters were not measured.

There are still gaps in knowledge that needs to be addressed in order to improve the surveillance for cardiomyopathy in CCS.[16] These gaps include 1) the use of echocardiographic parameters for early detection of cardiomyopathy, 2) the accuracy of biomarkers and ECG parameters to diagnose subclinical cardiac dysfunction, 3) the cardiotoxicity of non-anthracycline containing chemotherapy, such as high-dose cyclophosphamide, ifosfamide and vincristine,[3,5,13] 4) the role of genetics in the susceptibility for cardiomyopathy and 5) the combined use of blood biomarkers, ECG and echocardiography for the detection of subclinical cardiac dysfunction.

Considering these knowledge gaps, more information from echocardiography including myocardial strain, blood biomarkers (including genetics) and ECG measurements for the early detection of cardiac dysfunction in CCS and their associations with cancer treatment exposures is needed. In this paper we will describe the methodological aspects of the Dutch LATER cardiology study (LATER CARD) project that focusses on subclinical cardiac dysfunction in CCS who received (potential) cardiotoxic cancer treatment(s) as detected by echocardiographic parameters including myocardial strain, blood biomarkers and ECG parameters.

Figure 1



Flowchart of potentially eligible patients in the LATER CARD study. Cancer diagnosis dates of CCS in the LATER CARD study were between 1963 and 2001. Patient enrollment in the DCOG-LATER CARD study started in February 2017 and we are planning to include participants until March 2020.

Methods

Funding

The LATER CARD study is supported by grants from the Dutch Heart Foundation (CVON2015–21) and Kika/ODAS (grant 171 'DCOG LATER program').

Objectives

The main objectives of the LATER CARD study are to evaluate 1) the prevalence and associated (treatment related) risk factors of subclinical cardiac dysfunction in CCS compared to sibling controls and 2) the diagnostic value of echocardiography including myocardial strain and diastolic function parameters, blood biomarkers and ECG or combinations of them in the detection of cancer therapy-related cardiac dysfunction.

The LATER CARD study is subdivided into six work packages (WPs) with different objectives that support the main objective. WP1 consists of the data collection management that is required for the other WPs and does not address a specific research question. In WP2 we will study the prevalence and treatment related risk factors for subclinical systolic cardiac dysfunction including strain and diastolic LV dysfunction identified by echocardiography. WP3 concerns the prevalence of blood biomarker abnormalities and associated treatment related risk factors. In WP4 the prevalence and associated treatment related risk factors of abnormal ECG measurements will be studied. The diagnostic tools studied in WP 2, 3 and 4 will then be compared with respect to their diagnostic value in detecting subclinical cardiac dysfunction (see "Definitions" below). WP5 will study the gender differences in the prevalence of subclinical cardiac dysfunction, abnormal blood biomarker values and ECG abnormalities. In WP6 the results of all other WPs will be combined to formulate guideline recommendations for the cardiac surveillance of long-term CCS.

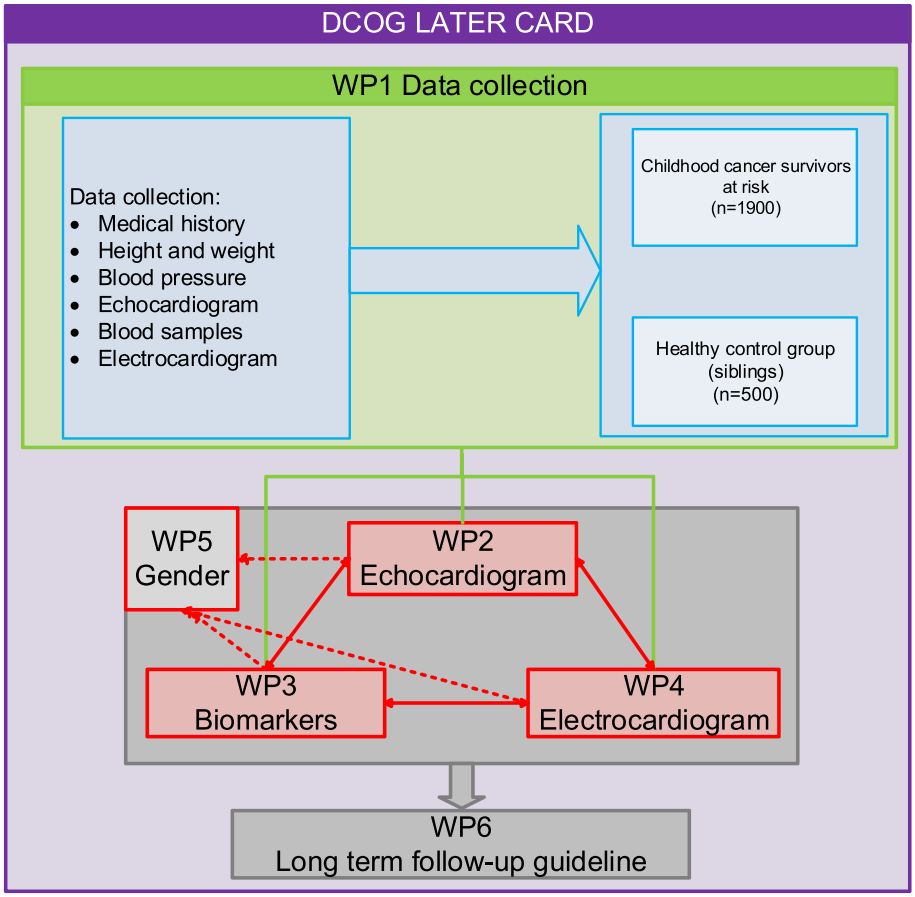
Study design

The Dutch LATER CARD study, is part of the Dutch Childhood Cancer Survivors Study LATER 2 study, a cross-sectional study of a retrospective nationwide cohort of 5-year CCS (Figures 1 and 2). The LATER study is a collaboration between 7 pediatric oncology centers in the Netherlands (Amsterdam University Medical Center (VU Medical Center and Academical Medical Center), Leiden University Medical Center, Erasmus Medical Center, University Medical Center Groningen, Radboudumc and University Medical Center Utrecht/Wilhelmina Children's Hospital/Princess Máxima Center for Pediatric Oncology) and includes a close collaboration with experts for specific health problems. The study protocol was approved by the medical ethic boards of all participating centers.

Study population

Informed consent is being obtained from all participants before study inclusion. The study population is

Figure 2



Study design of the LATER CARD study. The LATER CARD study is sub-divided in workpackages (WPs). WP1 consists of the data collection that is needed for the other WPs. The results of WP 2,3,4 and 5 will be used to improve the long-term follow-up guideline (WP6).

obtained from the Dutch LATER nationwide cohort (n = 6165), including all 5-year CCS diagnosed before the age of 18 years, between 1/1/1963 and 12/31/2001 with a malignancy according to the third edition of the International Classification of Childhood Cancer.[31] We only include CCS who were living in the Netherlands at the time of childhood cancer diagnosis and who were treated in one of the Dutch pediatric oncology centers.

In the LATER CARD study we will include CCS from the LATER cohort who were treated with (potentially) cardiotoxic cancer treatments. The LATER CARD study will include four risk groups; *risk group 1 (no maximum number)*: CCS 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).

As a comparison group 500 healthy *siblings* recruited from the participants will be included (Figure 1). We chose for siblings as the comparison group because they are of approximately the same age and share a partially common background risk for cardiac disease based on genetic make-up and early life influences.

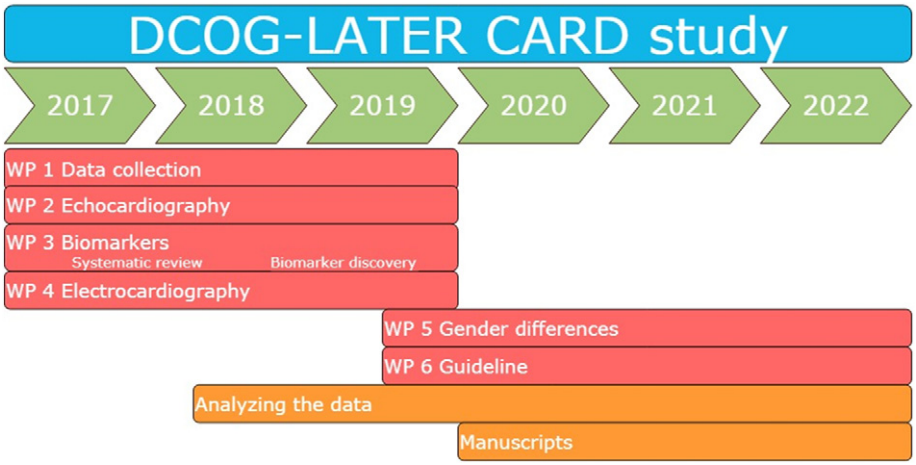
Study timeline

Patient enrollment in the LATER CARD study started in February 2017 and we are planning to include participants until 2020. We aim to finish all the analyses in January 2022. The specific timeline per WP is displayed in Figure 3.

Definitions

LV systolic dysfunction will be defined as a biplane EF <52% for males and a biplane EF <54% for females, in accordance with the European Association of Cardiovascular Imaging recommendations.[32] Specific subgroups of LV dysfunction

Figure 3



Timeline of the LATER CARD study and the different work packages (WP).

will be defined: Mid-range EF (EF 40–51% for males and EF 40–53% for females) and reduced EF (EF <40%).

LV diastolic dysfunction will be defined as grade > I diastolic dysfunction according to the European Association of Cardiovascular Imaging recommendations.[33]

Abnormal myocardial strain values will be defined based on age, sex and vendor specific normal values and the values obtained in the sibling controls.[34]

Data collection

The LATER CARD project is one of the 15 projects in the LATER study, each investigating different organ systems/topics (e.g. pulmonary, bone, cardiac, psychosocial, psychosexual). All study participants of the LATER CARD study will be invited once to the outpatient clinic in one of the pediatric oncology centers. A research physician will collect the following data for the LATER CARD study: (1) Medical history including family history of cardiovascular diseases, presence of hypertension, diabetes, hypercholesterolemia and life style factors such as alcohol use and smoking. (2) A comprehensive medical history including questions regarding dyspnea, chest pain, palpitations, dizziness, fainting episodes and peripheral edema. (3) Diagnostic tests: height and weight, blood pressure, echocardiographic measurements including measurements from the previous echocardiogram (if available), blood for biomarker sampling and a resting ECG. All data will be anonymized and stored in a central database.

Echocardiography. A standardized echocardiogram, will be performed in all CCS and sibling controls included in the LATER CARD study in the participating centers. Standard measurements (including LV dimensions, LV mass, FS, biplane EF, right ventricular dimensions and function, systolic pulmonary artery pressure, valve abnormalities, and diastolic function measurements) will be performed by experienced sonographers. In one of the participating centers 3-dimensional EFs will be measured. Additional echocardiographic views are obtained for strain analysis in the corelab. All measurements will be anonymized and saved on disc (DICOM format). The analyses will centrally be interpreted by the echocardiography corelab in the Radboudumc in Nijmegen, the Netherlands. The standard measurements will be reviewed and corrected by the corelab and additional measurements will be performed (including radial, circumferential and longitudinal systolic strain and strain rate, biplane EF, left atrial volume index and diastolic parameters including tissue Doppler imaging).

Blood sampling. In all CCS and siblings included in the LATER CARD study, venous blood (divided in plasma and cell portions) will be collected and stored at −80 degrees Celsius in the LATER biobank in Utrecht. Blood sample storage will be available for future biomarker evaluation including the evaluation of genetic susceptibility for cardiac dysfunction.

A panel of 184 protein biomarkers from different biological processes will be evaluated in a targeted proteomics study in a nested case–control format within the LATER CARD study cohort. The 184 markers are part of the Cardiovascular panel III and the Organ Damage panel from Olink Proteomics.

The biomarkers, their interactions and their corresponding biological processes are listed in Supplementary Table 1 and visualized in Supplementary Figure 1. Biomarker interactions and biological processes were obtained with STRING, a database which combines data on protein interactions and biological process classifications from different curated databases (GO, KEGG, Reactome).[35] The 184 biomarkers are mainly implicated

in (myocardial) cellular damage/apoptosis, hemodynamic load, inflammation, neurohormonal activation, oxidative stress, extracellular turnover/remodeling, platelet activation/thrombosis, endothelial dysfunction and lipid metabolism.[36]

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and biomarkers identified in the case–control study will be evaluated in the entire LATER CARD cohort for their diagnostic value (sensitivity, specificity, negative predictive value and positive predictive value) in detecting (subclinical) LV systolic dysfunction, abnormal myocardial strain and LV diastolic dysfunction on echocardiography.

Genetic analysis will include a genome wide association study to identify susceptibility loci for cancer-therapy related cardiac dysfunction. In addition, we will evaluate the prevalence of genetic variants that are associated with dilated cardiomyopathy in CCS with cancer-therapy related cardiac dysfunction and their contribution in the risk-stratification of CCS.

ECG. In all CCS included in the LATER CARD study and sibling controls, a 12-lead resting ECG will be performed. ECGs will be stored centrally and will be analyzed by the corelab according to the Minnesota criteria.[37]

Statistical analysis

Power analyses. The power calculations are performed with a power set at 80% and alpha set at 0.05. To detect a clinical significant difference in proportion of subjects with subclinical LV systolic dysfunction (assuming a proportion of 10% in CCS and 1.5% in the sibling controls) we need n = 128 in each group.

We assume that 13% of the CCS and 2.5% of the sibling controls will have abnormal NT-proBNP values, adjusted for age and sex.[38,39] Therefore, to detect a significant difference in proportion of abnormal NT-proBNP values between the CCS and the sibling controls we need n = 108 in each group.

To detect a clinically significant difference in proportion of major ECG abnormalities of 10% (estimated proportion in the sibling controls 2.8%[40]) between the CCS and the sibling controls we need n = 112 in each group. However, because we aim to perform subgroup analyses according to risk factors (gender, cancer treatment) more CCS and sibling controls will be included.

Prevalence analyses. The prevalence of LV systolic dysfunction (defined as a biplane EF <52% for males and <54% for females[32]), LV diastolic dysfunction (grades according to the European Association of Cardiovascular Imaging[33]) and abnormal myocardial strain (age, sex and vendor based normal values[34]) will be reported and compared between the different risk groups and with the sibling controls with the χ^2 test. Likewise, the prevalence of abnormal candidate blood biomarkers and major and minor ECG abnormalities (according to the Minnesota criteria[37]) will be reported.

Risk factor analyses. Risk factor analyses for LV systolic dysfunction, LV diastolic dysfunction, myocardial strain abnormalities, abnormal blood biomarkers findings and abnormal ECG measurements will be evaluated using separate multivariable logistic regression models including cancer treatment(s), follow-up time, sex, age at diagnosis, lifestyle factors (including smoking, alcohol consumption) and comorbidities (including hypertension, overweight, diabetes, hypercholesterolemia). The association between cancer treatment exposures and echocardiographic measurements (including EF, strain and diastolic function), blood biomarker values and ECG measurements will be evaluated with multivariable linear regression models.

Diagnostic accuracy analyses. The association between echocardiographic indices, blood biomarker values and ECG parameters will be tested in linear regression models. The diagnostic value of blood biomarkers and ECG parameters to detect LV systolic dysfunction, LV diastolic dysfunction or strain abnormalities will be evaluated with cut-off points derived from receiver operating characteristic curves. Optimal cut-off points for confirming or excluding the presence of LV systolic dysfunction, LV diastolic dysfunction or strain abnormalities will be reported with the sensitivity, specificity, positive predictive value and negative predictive value."

Subgroup analyses. Subgroup analyses will be performed in CCS without a (previous) diagnosis of congestive heart failure (as defined by the European Society of Cardiology heart failure guideline).[19]

To detect early markers for subclinical cardiac dysfunction subgroup analyses will be performed in asymptomatic CCS with a normal LV function at the previous echocardiogram (within 5 years, if available) and without symptoms of heart failure.

Additional subgroup analyses will be performed for males and females to evaluate gender differences in prevalence and risk factors for cardiac dysfunction.

Non-normally distributed variables will be log-transformed or tested for with the use of non-parametric tests. Two sided p-values <0.05 will be considered as statistically significant.

Preliminary results

Study population

Table I presents the characteristics of all eligible CCS and sibling controls for the LATER CARD study who were alive on January 1, 2017. The eligible study cohort includes 3608 CCS and 1066 siblings, the majority of CCS had a primary diagnosis of leukemia, lymphoma, renal tumors, bone or soft tissue sarcomas. There are 2566 eligible CCS in *risk group 1*, 48 eligible CCS in *risk group*

Table I. Patient, cancer and treatment characteristics of eligible 5-year survivors for the DCOG-LATER CARD cohort and sibling controls.*

	Potential study population (n = 4674)	
Characteristics	Childhood cancer survivors	Sibling controls
n	3608	1066
Sex		
Female	1530 (42.4%)	452 (42.4%)
Male	2078 (57.6%)	614 (57.6%)
Primary childhood cancer (ICCC)		
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	1641 (45.5%)	-
Lymphomas and reticulo-endothelial neoplasms	783 (21.7%)	-
CNS and miscellaneous intracranial and intraspinal neoplasms	150 (4.2%)	-
Neuroblastoma and other peripheral nervous cell tumors	85 (2.4%)	-
Retinoblastoma	1 (0.0%)	-
Renal tumors	430 (11.9%)	-
Hepatic tumors	36 (1.0%)	-
Bone tumors	226 (6.3%)	-
Soft tissue and other extraosseous sarcomas	185 (5.1%)	-
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	61 (1.7%)	-
Other malignant epithelial neoplasms and malignant melanomas	8 (0.2%)	-
Other and unspecified malignant neoplasms	2 (0.0%)	-
Age at cancer diagnosis (year)		
0–4	1663 (46.1%)	-
5–9	989 (27.4%)	-
10–14	749 (20.8%)	-
15–17	207 (5.7%)	-
Cancer treatment period		
1963–1979	442 (12.3%)	-
1980–1989	1149 (31.8%)	-
1990–2001	2017 (55.9%)	-
Overall treatment modality		
Risk group 1: Anthracyclines/mitoxantrone and/ or chest RT	2566 (71.1%)	-
Risk group 2: Cyclofosfamide only	48 (1.3%)	-
Risk group 3: Ifosfamide only	33 (0.9%)	-
Risk group 4: Vincristine only	961 (26.6%)	-

Chest RT = radiation therapy involving the heart region.
* Percentage of the total DCOG-LATER CARD cohort including sibling controls

2, 33 eligible CCS in *risk group 3* and 961 eligible CCS in *risk group 4* (Figure 1).

Inclusion

We expect to include 1900 of the 3608 CCS and 500 of the 1066 siblings (total study population = 2400) in a consecutive order. Currently (May 2019), we have collected data of 1283 CCS and 189 siblings.

Expected results

With the LATER CARD study we will report the prevalence and relative risk of subclinical cardiac dysfunction in CCS compared to sibling controls based on echocardiographic imaging (including abnormal myocardial strain and LV diastolic dysfunction parameters), blood biomarkers and ECG parameters and their associations with treatment and gender related risk factors.

Furthermore, we will determine the value of myocardial strain, blood biomarkers and ECG parameters in the diagnosis of LV dysfunction and their prognostic usefulness in the surveillance of long-term CCS at risk for heart failure (from subgroup analyses of patients with a prior normal echocardiogram).

In addition, we expect to provide evidence on the cardiotoxicity of cyclophosphamide, ifosfamide and vincristine. However, given the low number of CCS in the cyclophosphamide only and ifosfamide only group (48 and 33), collaboration with other childhood cancer survivors cohorts is likely to be necessary before definite conclusions can be drawn on the cardiotoxicity of these agents.

Hereby the LATER CARD study will form the basis of an improved surveillance guideline in long-term CCS.

Discussion

In the LATER CARD study, we will investigate the single and joint contributions of diagnostic tools to detect cancer therapy-related cardiac dysfunction in a large long-

term CCS cohort treated with cardiotoxic cancer therapies. The diagnostic tools (myocardial strain, diastolic function parameters including tissue Doppler measurements, blood biomarkers and ECG) that we will study are scarcely investigated in large long-term CCS cohorts[9,16,27,28,30] and were not previously studied in relationship with each other or compared with sibling controls.

Two-dimensional EF, measured with echocardiography, is the most frequently used parameter in the surveillance of long-term CCS for cancer therapy-related cardiac dysfunction but is limited by its reproducibility, load dependency and inability to detect subtle changes in EF.[21,41] From studies in adult oncology patients, we know that early detection of subclinical cardiac dysfunction is necessary to prevent cardiac deterioration, by initiating treatment with heart failure medication.[18] Adopting this view, sensitive markers are needed that are able to detect early signs of cardiac deterioration before heart failure symptoms occur.

Although, evidence of the diagnostic tools (EF, longitudinal strain, diastolic function, NT-proBNP and high sensitive troponins) on future development of heart failure in long-term CCS is lacking, they are established predictors for heart failure in the general population.[23,26,42,43] Therefore, by extrapolating these findings to CCS we expect that the diagnostic tools evaluated in the LATER CARD study can identify CCS at higher risk for development of heart failure, and thus bring benefit from more frequent surveillance and/or early treatment initiation. Importantly, the results may also identify CCS at low risk for heart failure in whom we can decrease the surveillance frequency.

In addition, with sub-group analyses of patients with a normal prior echocardiogram we may infer the role of these diagnostic tools in the natural history of cancer therapy-related cardiac dysfunction.

A limitation of the LATER CARD study is that it is of cross-sectional nature and therefore may not be able to validate the findings in predicting future cardiac dysfunction in those patients that do not have cardiac dysfunction or only minor signs of them. The study is therefore mainly able to discern those patients with early or progressed LV dysfunction from those with no dysfunction and therefore mainly to diagnose or exclude the presence of clinically important LV dysfunction with either of the diagnostic tools. As the study is conducted in a large cohort of CCS who previously received regular surveillance by echocardiography according to prevailing guidelines,[10] we may be able to identify which markers are markers of progression for cardiac dysfunction and provide additional evidence for risk assessments. Still, future follow up studies of our cohort will be needed to confirm the value of the described diagnostic tools as early markers for clinical heart failure in long-term CCS. Furthermore, the number of patients eligible for the cyclophosphamide only and ifosfamide only group was limited, as treatment with these agents alone is rare. Future collaborations with other long-term childhood cancer survivor cohort may be necessary to draw definite conclusions on the cardiotoxicity of these agents.

Eventually, the results of the LATER CARD study will provide the evidence to improve long-term follow up guidelines, which we aim to complete at the end of this project. Furthermore this project will form the basis for future prospective follow-up studies that will increase the knowledge on the predictive value of the described tests. This project will be carried out by a multidisciplinary team of caregivers and researchers in the field of cancer therapy-related cardiac dysfunction in long-term CCS. This team will enable the implementation of the improved guideline recommendations in a broad field of health professionals involved in the care for CCS.

Conclusion

The Dutch LATER CARD study will investigate diagnostic tools to detect subclinical cardiac dysfunction in long-term CCS treated with potential cardiotoxic cancer therapies. This will be an important study to investigate the relationship between clinical data, echocardiographic, blood biomarker and ECG measurements to detect cardiac dysfunction in a large nationwide cohort of CCS. The results will form the basis of an improved long-term follow up guideline to ultimately prevent heart failure in this population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.10.010.

Acknowledgements

We thank Bep Verkerk and Martine Raphael for their contributions at the LATER registry and coordinating office as well as all data managers in the seven participating centers and Aslihan Mantici for obtaining the data for this study. Furthermore, we thank Margreet Veening for her contributions as a late effects outpatient clinic physician and Lideke van der Steeg for her contribution as a LATER board member. We would also like to thank all cancer survivors and siblings participating in the study and the VOKK and VOX for their contribution to the LATER CARD study.

Data sharing statement

Individual participant data, after de-identification, may be shared with investigators who would like to collaborate after the main analyses of the LATER CARD study are finished. Applications of intent can be sent to e.a.m.feijen@prinsesmaximacentrum.nl and will be reviewed by the LATER study group.

Disclosures

None declared.

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