Clinical evaluation of late outcomes in Dutch childhood cancer survivors: methodology of the DCCSS LATER study part 2

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Abstract

Background Childhood cancer survivors face late health problems; despite advances in research, details on risk remain unclear. We describe the methodological aspects of the Dutch Childhood Cancer Survivor Study (DCCSS) cross-sectional clinical study (LATER 2 study). Procedure From the multi-center DCCSS LATER cohort of 6,165 five-year survivors diagnosed 1963-2001, we invited 4,735 eligible in 2016, as well as siblings and parents of survivors. Gaps in evidence identified during development of surveillance guidelines were translated into clinical research questions for 16 outcome-specific sub-projects. The regular care visit to the LATER outpatient clinic forms the backbone of outcome assessment complemented with research-defined measurements (physical examination, diagnostic tests, questionnaires). Furthermore, blood/saliva samples were taken for DNA extraction. Results In total, 2519 (53.2%) survivors participated in the LATER 2 study. Of those participating survivors, 49.3% was female. Median time since childhood cancer diagnosis was 26.9 years (range 14.8 to 54.7 years) and median attained age was 34.4 years (range 15.4 to 66.6 years). Conclusions The high-quality data generated in the LATER 2 study will provide valuable insights into risks of and risk factors for clinical and (psychosocial) health outcomes and factors for early recognition

of (psychosocial) health outcomes in long-term childhood cancer survivors. This will contribute to fill in important gaps in knowledge and improve the quality of life and care for childhood cancer survivors.

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Childhood cancer survivors, methodology, late outcomes, clinical study, questionnaires

Abbreviation table

Abbreviation	Full term or phrase
DCCSS	Dutch Childhood Cancer Survivor Study
BRP	Municipal Personal Records Database (Dutch: Basisregistratie Personen)
DXA	Dual-energy x-ray absorptiometry
DNA	Deoxyribonucleic acid
NPV	Negative predictive value
PPV	Positive predicted value
IGHG	International Guideline Harmonization Group

Abstract

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Results In total, 2519 (53.2%) survivors participated in the LATER 2 study. Of those participating survivors, 49.3% was female. Median time since childhood cancer diagnosis was 26.9 years (range 14.8 to 54.7 years) and median attained age was 34.4 years (range 15.4 to 66.6 years).

Conclusions The high-quality data generated in the LATER 2 study will provide valuable insights into risks of and risk factors for clinical and (psychosocial) health outcomes and factors for early recognition of (psychosocial) health outcomes in long-term childhood cancer survivors. This will contribute to fill in important gaps in knowledge and improve the quality of life and care for childhood cancer survivors.

Introduction

Advances in diagnosis and treatment of childhood cancer over the last decades have dramatically increased long-term survival, with a 5-year overall survival of more than 80%.[1] As a result, the number of childhood cancer survivors is growing and it has become increasingly clear that the former disease and its treatment can significantly impair long-term (psychosocial) health leading also to premature mortality.[2-5]

In 2010 the Dutch Childhood Cancer Survivor Study (DCCSS) LATER collaborative group finalized the LATER guideline for surveillance of late effects in survivors of childhood cancer and identified clinically-relevant gaps in knowledge.[6] The DCCSS group of clinicians, researchers, and representatives from the patient-parent organization designed the DCCSS LATER cohort study, currently consisting of 2 parts (Figure 1). In the LATER 1 observational study, outcomes on health conditions were collected, through questionnaires and linkages to national registries. The methods for this study have been described in a separate paper.(Teepen et al. Joint submission with current manuscript)

Here we describe the methodology and first results of the second wave of health outcome measurements, the so-called LATER 2 study, which involves clinical measurements.

All cohort members alive in 2016 were invited to participate in this cross-sectional study, the backbone of which consists of the periodic guideline-based regular care visit to the late effects outpatient clinic.

The goals of the LATER 2 study are A) to identify and characterize populations at high risk for medical and/or psychosocial chronic health conditions associated with childhood cancer, its treatment, and other risk factors such as lifestyle, B) to identify accurate screening tests for adverse health outcomes in survivors of childhood cancer, C) to get insight into the pathophysiological mechanisms and genetic predisposition underlying the multi-factorial etiology of the studied health outcomes, D) to identify groups of survivors who may benefit from interventions and preventive measures and to identify subgroups who will likely not benefit from such actions.

To achieve these goals, the DCCSS LATER study group designed, a priori, 16 sub-studies based on health outcomes (Supplemental information Table 1). Eligible survivors were invited to undergo diagnostic tests and questionnaires for research purposes, in addition to the diagnostic tests during regular care, based on the LATER guidelines. This paper describes the methodological aspects of the overall LATER 2 study; clinical visit & questionnaire study. The specific methodologies of sub-studies will be described in separate papers.

Methods

The DCCSS LATER 2 study is a cross-sectional study within the multi-center LATER cohort of 6,165 five-year survivors of childhood cancer, who were initially diagnosed between 1963-2001. (Teepen et al. submitted) in the seven pediatric oncology centers in the Netherlands (Amsterdam University Medical Center (VU Medical Center and Academic Medical Center), Leiden University Medical Center, Erasmus Medical Center Rotterdam, University Medical Center Groningen, Radboudumc Nijmegen and University Medical Center Utrecht). Since 2018, is pediatric oncology care centralized in the new Princess Máxima Center.

Participants LATER 2 study

Childhood cancer survivors

Survivors included in the LATER cohort were traced via the Municipal Personal Records Database (Dutch: Basisregistratie Personen [BRP]) to identify their vital status and most recent address. All survivors confirmed alive and with a known address in the Netherlands were eligible for invitation. Survivors who were lost to follow-up, living abroad, objected to participate in any scientific research, or who were considered ineligible to participate by their late effects physician (e.g. on active cancer treatment) were excluded.

Siblings & Parents

Siblings identified during the LATER 1 study were also invited to participate in the LATER 2 study for selected research questions (for questionnaires and echocardiogram, electrocardiogram, and cardiac biomarkers). Parents of the invited survivors were invited to participate in the psycho-oncology questionnaire study (see also Supplemental information Table 1).

Invitation process

Within the web-based LATER study database, we developed a tool to automatically support the invitation process and logistics for the outpatient clinical visit during the period February 2016-February 2020. A tailor-made study invitation was generated to facilitate the informed consent for participation to all eligible survivors according to the outpatient clinic where the survivor was known (Amsterdam University Medical Center (location VUmc), Leiden University Medical Center, Erasmus Medical Center, University Medical Center Groningen, Radboudumc and Princess Máxima Center for Pediatric Oncology). A unique feature of this application is that the program assigned each survivor to the appropriate study arms for all 16 sub-studies, based on the characteristics of the survivor, his/her previous childhood cancer diagnosis and treatment, and the center from which he or she participated. If a survivor agreed to participate, study tests

were planned in combination with an already planned outpatient visit. If a survivor did not respond to the initial invitation, the local center sent a reminder or attempted to establish contact to the survivor by phone. To optimize and standardize information for all centres study, manuals were developed concerning the logistics, data collection procedure, and storage of material. The study protocol for all LATER 2 sub-studies were approved by the medical ethics boards of all participating centers.

Data collection

For all 6,165 five-year childhood cancer survivors in the underlying LATER cohort, detailed information on childhood cancer diagnosis and treatment for the primary cancer and all recurrences was collected from the historic medical records, prior to this study. (Teepen et al. submitted) The overall concept of data collection for the LATER 2 study is summarized in Supplemental information Table 2 and Table 3, and alluded to below.

Physical Examination

During the out-patient clinic visit, for both survivors and their siblings we collected data on height, sitting height, weight, waist circumference, hip circumference, blood pressure (three measurements, of which the last two were registered), and pulse. In addition, among survivors we assessed pubertal stage (in survivors <18 years of age), a skin examination was performed, as well as, thyroid palpation, and an assessment of testicular volume among males.

Diagnostic tests

In the LATER 2 study, participating survivors were invited for a number of diagnostic tests, the extent of which was based on age, sex, prior treatment, and participating center. In total, a maximum of seven (functional) tests targeting different health outcomes / organ systems were performed, including dual-energy x-ray absorptiometry (DXA) scan, echocardiogram, electrocardiogram, 6-minutes walking test, hand grip test, pulmonary function test, and 24-hour blood pressure. Some siblings were invited to undergo echocardiogram and electrocardiogram.

Questionnaires

Participating survivors and siblings were asked to complete an updated questionnaire on general health and lifestyle. Survivors and siblings who participated in the LATER 1 questionnaire study in 2012—2014 (Teepen at al. submitted) received an abbreviated version of this questionnaire focusing on main health outcomes only (Supplemental information Table 3). Several other outcomes were assessed with, mostly validated, questionnaires (Supplemental information Table 4). Each survivor was invited to complete outcome-specific questionnaires for sub-studies for which the survivor was eligible. Questionnaires were spread in time (before, during and after the outpatient clinic recruitment visits) in order to limit the burden for survivors. Siblings of survivors also received questionnaires on psychosocial outcomes, fatigue, and skin health and parents of survivors received questionnaires on psychosocial outcomes.

Bio-Material

To obtain DNA, a blood or saliva sample was collected, DNA was extracted and stored in the LATER study biobank. Additional blood samples were drawn from survivors and siblings and stored in -80°C in several aliquots for study questions and future central analyses. For specific outcomes (renal and splenic function), blood was analyzed directly in the lab of the local center. For some sub-studies, we also collected a semen specimen, urine sample, and saliva sample.

Monitoring of the quality of study participation and communication

The LATER Central Office developed an extensive data and procedural monitoring program on informed consent procedures and documentation as well as data registration, which started after the inclusion of the first two survivors per center. Annual monitor visits were held at each center, followed by a monitor visit report. This report entailed a summary of the findings, recommendations for improvement, and a list

of actions to be resolved. Inclusion rates for all centers and all sub-studies were calculated and visualized quarterly, to monitor sub-study inclusions and to allow for comparison with pre-defined targets. Based on these data, a (subgroup of a) sub-study was closed when a respective study arm was full. In addition to the annual site monitoring, the Central LATER office implemented ongoing monitoring on selected items and activities in all centers, in order to facilitate local sites to continuously improve data quality.

Statistical analyses LATER 2 sub-studies

Comparing participants and non-participants

To analyze potential differences between participants and non-participants, each sub-study will summarize sex, age at diagnosis, type of cancer, attained age and cancer treatment for participants and non-participants, using Student's t-tests (for normally distributed data) or Mann Whitney U test (for non-normally distributed data) when variables are continuous and Chi square test (if n[?]5) or Fisher's exact test (if n<5) when variables are categorical.

Prevalence of outcomes and risk factor analyses

The prevalence of an outcome, expressed as percentage, will be calculated by dividing the number of cases by the total number of participants (for that specific study) multiplied by 100. The 95% confidence intervals (95% CI) will be calculated by the Wilson method. When there is more than one subgroup of survivors or when a control group is included, the proportion of the cases in the separate groups will be compared with a Chi squared test. Subsequently, the respective contributions of risk factors, and their single and, where feasible, joint effects on the prevalence of respective outcomes will be estimated using multivariable regression analyses. Per health outcome, the possible determinants will be selected based on clinical knowledge and previous literature. For each covariate a direct analytical graph will be made to assess whether it is a (proxy) confounder, mediator, collider or competing exposure. To prevent overcorrection, cancer treatment and type of cancer will not be evaluated in the same model as they are strongly correlated.

Diagnostic value of a diagnostic test

For sub-studies focusing on the diagnostic value of a particular diagnostic test, the negative predictive value (NPV), positive predicted value (PPV), sensitivity and specificity will be calculated. The NPV represents the number of true negatives divided by the negative calls (true negative + false negative). The PPV is the number of true positives divided by the positive calls. Sensitivity is the proportion of people who test positive among all those who actually have the disease and is calculated by dividing the true positive by the true positive plus false negative. Specificity is the proportion of people who test negative among all those who actually do not have that disease, and is calculated by dividing the true negative and the true negative plus false positive.

Statistical analyses current paper

In the current paper, we compared the participants and non-participants by sex, age at diagnosis, type of cancer, attained age (age at invitation), follow-up time since childhood cancer diagnosis until invitation, and for cancer treatment (dichotomous variables for any chemotherapy, any radiotherapy, any surgery and categorical variable for bone marrow/stem cell transplant [no, autologous, allogenic, unknown]). Treatment variables represent cumulative exposures accumulated during treatment for primary tumor, metastases and recurrences, regardless of time since first diagnosis, and captured from original medical files in the treatment centers (e.g. Teepen et al. submitted). Differences in the distributions were tested using a Chi square test.

Results

Characterization of participants

In Figure 2 the recruitment process is summarized. For the LATER 2 study, we started with 5,139 potentially eligible survivors alive October 10, 2016. After careful tracing and assessment, we excluded 418 individuals

for the following reasons: 99 survivors died between the recruitment periods of the LATER 1 and LATER 2 study, 55 survivors were lost to follow-up, 179 survivors were living abroad, 47 survivors were considered ineligible for participation in the LATER 2 study by their physician, and 38 individuals were not invited due to other reasons constituting exclusion criteria (e.g. not proficient in Dutch language). In all, 4,735 survivors were invited for the LATER 2 study. In total, 2,519 (53.2%) of eligible survivors participated in the study, 744 survivors declined participation, 1,472 survivors did not respond to the invitation and the reminders. Of the participating survivors, 127 signed the informed consent, but eventually did not participate in additional data collection for the study. For this group, we were able to extract data from the medical records from their regular late effects outpatient clinic visit and use this for some of the research questions in the study.

In Figure 3 the planned and realized trend-lines of invitation and out-patient clinic visit are shown. Although the participation rate was initially lower than expected, we eventually included our intended number of 2,500 survivors. In addition, 541 (36.1%) of 1,499 invited siblings and 661 (66.4%) of 996 invited parents participated in the LATER 2 study.

Table 1 presents demographic information, tumor characteristics, treatment and follow-up information of the survivors who participated in the LATER 2 study. Of the 2,519 participating survivors, 49.3% was female (n=1,242). Median follow-up time since childhood cancer diagnosis was 26.9 years (range 14.8 to 54.7) and median attained age was 34.4 years (range 15.4 to 66.6 years). The majority of the participating survivors had been diagnosed with leukemia, myeloproliferative disease and myelodysplastic disease (35.6%), lymphoma and/ or reticuloendothelial neoplasm (18.9%) and renal tumor (11.3%). For treatment of primary cancer or recurrences, 13 (0.5%) survivors did not have any recorded surgery, chemotherapy or radiotherapy (mainly neuroblastoma stage IV's and low grade CNS tumors, which sometimes have a wait and see policy), 163 (6.5%) survivors received surgery only, 1,375 (54.6%) survivors received chemotherapy only (with or without surgery), 133 (5.3%) survivors received radiotherapy only (with or without surgery) and 834 (33.1%) survivors received both chemotherapy and radiotherapy (with or without surgery). Of participating survivors, 166 (6.6%) had received a bone marrow transplant, of which 57 (2.3%) were autologous and 109 (4.3%) were allogenic. When comparing participants with non-participants (Table 1) in univariate analyses, we observed that females were more likely to participate than males ($p<0.00001$), CNS survivors were less likely to participate compared to other cancer types ($p <0.00001$), and survivors treated with chemotherapy and radiotherapy were more likely to participate compared to other survivors.

Diagnostic tests, questionnaires, and bio-materials

In Table 2, the numbers of participants who underwent specific diagnostic tests are displayed.

The following diagnostic tests were performed: 104 24-hour blood pressures, 311 6-minute walk tests, 1,657 DXA scans, 1,352 echocardiograms, 1,385 electrocardiograms, 1,816 hand grip tests, and 586 pulmonary function tests. The LATER questionnaire was completed by 2,229 survivors (n=473 full / n=1,756 short repeat questionnaire, see Methods section for explanation). Almost 70% of the participating survivors also completed the extensive test battery concerning psychosocial outcomes (data not shown). The following bio-materials were obtained: 2,257 blood samples, 271 saliva specimens, 657 semen specimens, 979 urine samples. In total, we extracted DNA for 2,270 survivors, i.e. 90.1% of all participating survivors. Among siblings, we collected 277 echocardiograms, 272 electrocardiograms, and 278 blood samples.

Discussion

In this paper, we described the methodology, participation rates, and data availability of the DCCSS LATER 2 study. With the clinical data collected in the LATER 2 study, we will be able to fill gaps in knowledge that have been identified in the published recommendations of the International Guideline Harmonization Group (IGHG).[7]

The LATER 2 study collected extensive data on clinical outcomes and questionnaires for 2,519 childhood cancer survivors, 632 siblings and 580 parents. The data collection was finished in 2020. An important strength of our study is that we evaluated objective clinical outcomes by diagnostic tests using blood and

urine samples in combination with functional tests, and therefore do not rely solely on self-reported outcomes, which can be prone to recall bias. Another strength is that we used validated questionnaires for our outcomes. Furthermore, by including siblings for some outcomes, we will be able to compare prevalence of outcomes and with a control group. The availability of detailed information on childhood cancer diagnosis and treatment enables in-depth analyses on potential risk factors for clinical outcomes.

In the LATER 2 study there is a risk of participation bias, as we found some differences between participants and non-participants in sex, type of cancer, and as a result also in childhood cancer treatment. This might under- or overestimate the prevalence of health outcomes. The consequences of these differences may vary between outcome-specific sub-studies. Therefore, differences between the participants and non-participants will be tested for each sub-study to evaluate specific patterns of potential (participation) bias specific to the health outcomes evaluated per sub-study.

The collected clinical data will be a repository for future studies. After completion of the primary studies on the a priori-defined clinically relevant research questions, we will combine data from different sub-studies, e.g. metabolic syndrome and cardiac diseases and quality of life related to medical outcomes, to answer further questions, which may also include health outcomes ascertained using record linkage in the LATER 1 study (e.g. benign and malignant tumors). In the future, it will be also be possible to link clinical parameters measured during the LATER 2 study to health outcomes that occur later.

The current study is one of the largest clinical study among childhood cancer study and includes a large variety of clinical outcome data collected in all types of childhood cancer survivors. As far as we are aware, the St. Jude Lifetime Cohort study represents the only other endeavor of this scale covering the full spectrum of childhood cancer types in which the burden of clinical outcomes is ascertained during a clinical visit.[8] Future collaboration will be important to improve knowledge on rare health outcomes.

In summary, in the LATER 2 study extensive information on various clinical and (psychosocial) health outcomes has been assessed during an outpatient clinic visit in a large group of childhood cancer survivors. The high-quality data will provide valuable insights into risks of and risk factors for clinical and (psychosocial) health outcomes and factors for early recognition of (psychosocial) health outcomes in long-term childhood cancer survivors. With this information, we will contribute to important gaps in knowledge and finally improve the quality of life and care for childhood cancer survivors.

Conflicts of interest statement

The authors have declared no conflicts of interest

Data accessibility

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figure legends

FIGURE 1 Overview of the DCCSS LATER cohort and specific study parts

FIGURE 2 Flowchart of invitation process and participation of survivors, siblings and parents in the DCCSS LATER 2 study

FIGURE 3 The planned and realized trend-lines of invitation and out-patient clinic visit

Tables

TABLE 1 Baseline characteristics Dutch LATER cohort.

TABLE 2 Diagnostic tests for the different outcomes, and the number of childhood cancer survivors and siblings participated in the tests.

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`Table 1.docx` available at https://authorea.com/users/482419/articles/568986-clinical-evaluation-of-late-outcomes-in-dutch-childhood-cancer-survivors-methodology-of-the-dccss-later-study-part-2

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