Childhood cancer survivors: cardiac disease & social outcomes
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Citation for published version (APA):

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Introduction and outline thesis
Childhood cancer

Malignancies that occur in children (age 0-17 years) represent only 1% of the annual malignancy incidence in developed countries, it is a unique subgroup with respect to both type of malignancy and survival. The most common types of pediatric cancer are leukemia, lymphoma and brain tumors, in adults however the most common types are carcinoma of the breast, gastro-intestinal tract and lung, which are extremely rare in children. Childhood cancer 5-year survival rates are among the highest in oncology and have improved considerably, from 20% in the 1940s to 70-80% at present. Childhood cancers are treated with surgery, radiotherapy, chemotherapy, and supportive therapy. It is well established that these treatments induce chronic health conditions in childhood cancer survivors (CCS).

Owing to the better survival over the years, the survivor population continues to grow in magnitude. These survivors often develop serious chronic health conditions.

Chronic health conditions

It is known, that after a median follow-up time of 17 years post-diagnosis, around 75% of the 5-year CCS will have at least one chronic health condition. The estimated cumulative prevalence of serious/disabling or life threatening chronic conditions in CCS at 45 years of age was reported to be is 80% (95% CI:73%-87%) in a large cohort of 10-years survivors. Previous research has shown that elevated rates of chronic health conditions among CCS translate into an increased likelihood of hospitalizations, i.e. contribute to higher healthcare consumption. The most common chronic health conditions are second primary malignancies, chronic cardiac health conditions/ cardiac events (CEs), endocrine, fertility and psychosocial/ cognitive problems.

Follow-up guidelines for chronic health conditions

Early detection and treatment of these chronic health conditions are of importance to prevent further health problems. Long term follow-up guidelines are necessary to ensure that all CCS receive “individualized” follow-up care they require. In March of 2010 the task force LATER of the Dutch Childhood Oncology Group developed a long term follow-up
guideline for optimal care of CCS more than 5 years after diagnosis.\textsuperscript{12} Twenty-two of the most common or serious chronic health conditions are covered in this guideline. To come to a recommendation, organ-specific working groups summarized available literature and answered the following working questions; 1) What is the incidence of these health problems and is this more common than in the normal population? 2) What are risk predictors? 3) What is the time course? 4) Are the diagnostic procedures accurate to reveal treatable diseases at an early stage? 5) Is there an effective treatment? This guideline has been implemented in clinical practice in the seven long term follow-up outpatient clinics in the Netherlands.

In this thesis we will focus on chronic cardiac health problems and social outcomes in CCS.

**Chronic cardiac health conditions**

CEs are among the most common and serious chronic health conditions after childhood cancer treatment. There are different types of CE; the most common of which is heart failure. It presents as either diastolic or systolic dysfunction, which may progress to dilated or constricted cardiomyopathy, and the heart failure can be asymptomatic or symptomatic. The cumulative incidence of *symptomatic* heart failure, 30 years after diagnosis, has been reported to be 2.7\%-4.1\% in a cohort of CCS.\textsuperscript{13,14} The cumulative incidence of *asymptomatic* heart failure, at median 15 years after diagnosis, has been reported to be as high as 27\%.\textsuperscript{15} Cardiac ischemia can be divided in two groups: “chronic” ischemia, in which one or more arteries are narrowed, causes oxygen deprivation in large parts of the heart, which subsequently kills the cardiac tissue. Myocardial infarction, in which an artery is fully occluded and will cause instant death to the cardiac tissue behind the artery. “Chronic” ischemia, can be asymptomatic and even without any electrocardiogram changes;\textsuperscript{16} a myocardial infarction is almost always associated with symptoms. The cumulative incidence of myocardial infarction, 30 years after diagnosis, has been reported to be 0.8\%-1.3\%.\textsuperscript{13,14} The cumulative incidence of “chronic” ischemia, has been reported to 16\%-39\%.\textsuperscript{17,18}
The spectrum of involvement of the pericard is broad and includes pericardial effusion, acute pericarditis, pericardial fibrosis, and constrictive pericarditis. The cumulative incidence of pericardial disease in CCS, 30 years after diagnosis, has been reported to be 3.0%. The cumulative incidence of symptomatic valvular disease, defined as severe or life-threatening or disabling valvular disease requiring treatment, 30 years after diagnosis, has been reported to be 0.6%-4.0%. A recent study of van der Pal et al. even reported that 31% CCS had 1 or more valvular abnormalities mild or higher with a median follow-up time of almost 15 years.

The incidence of arrhythmias, such as (supra)ventricular premature complexes, (supra)ventricular tachycardia, after childhood cancer treatment is largely unknown; reported frequencies are as high as 66%. which is substantially higher than in the general population. Patient related risk factors that increase the risk of developing a CEs include female gender, age at diagnosis, and having a congenital heart disorder. However the main risk factors for developing CEs are treatment with anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin and/or anthraquinone (i.e. mitoxantrone)) and radiation therapy involving the heart region. The mechanism of anthracycline-associated cardiac damage is not fully understood, it is clear that free radicals play an important role in damaging cardiac myocyte membranes. Some studies addressed cardio protective strategies; such agents can be given concomitant to anthracyclines. This can be given concomitant to anthracyclines. The most researched is dexrazoxane, a free radical scavenger, which seems to reduce early cardiotoxicity during doxorubicin treatment. Other strategies for example, continuous infusion, angiotensin-converting-enzyme (ACE) inhibitor, coenzyme Q10 and carnitine have not been well-studied, and results are inconsistent. Radiation-associated cardiac damage originates in micro vascular changes, which eventually result in fibrosis mainly in the interstitial part of the myocardium. Also inflammatory processes play an important role, in particular after low doses. There are, however, also CCS who will develop CE without being treated with the established potential cardiotoxic therapies. This can be the
result of two things; the cardiac event develops irrespective of the cancer treatment, since every person is at a certain risk for developing a cardiac event even without having had established cardiotoxic medical exposures. Or there might be as of yet other potential cardiotoxic treatments that have not been confirmed risk factors yet. For example the impact of other cytostatics, such as (high-dose) cyclophosphamide, has not been examined in large studies.\textsuperscript{32-35} This category also includes other types of treatment such as splenectomy\textsuperscript{36-38} or the influence of nephrotoxicity on the heart\textsuperscript{39}. Furthermore, recent studies suggested a possible association between genetic factors and anthracycline-induced cardiac dysfunction.\textsuperscript{40,41}

**Social outcomes**
As a consequence of the high risk of chronic health conditions in childhood cancer survivors, there is concern about the social development and outcomes in this group. Several studies show a worse social functioning (e.g. probability of marriage, living situation and social benefits) among CCS compared to the general population\textsuperscript{42-45} which can negatively affect the quality of life of CCS.\textsuperscript{46} This worse social functioning could be directly linked to the childhood cancer\textsuperscript{42,45,47}, but could also be the result of the chronic health condition like infertility and the psychosocial problems.\textsuperscript{48-50} The current follow-up guideline from the task force LATER of the Dutch Childhood Oncology Group\textsuperscript{12} includes psychosocial assessment for CCS.

**Objectives and outline of the thesis**
The thesis covers two themes, i.e., chronic cardiac health conditions and social outcomes in CCS; the general aims of part 1 were to create optimal conditions for the evaluation of chronic cardiac health conditions (CE) in 5-year childhood cancer survivors (CCS), and apply this research in an evaluation of the long term risk of CEs in Dutch childhood cancer survivors, and to uncover the associated (new) risk factors. Knowledge on incidence and risk factors has implication on treatment (protocols) of future childhood cancer patients, but also for the development of Long term follow-up guidelines.
Chapter 2 includes the protocol for a Cochrane systematic review on clinical heart failure in children, adolescents and young adults treated with anthracyclines and/or radiation therapy involving the heart region. Chapter 3 reports on a study in which we sought to determine the optimal anthracycline cardiotoxicity equivalence ratio based on the actual risk of HF observed in childhood cancer survivors, using data from four large well-annotated childhood cancer survivor cohorts with extensive follow-up. In chapter 4 we describe a newly developed method to grade CEs; a set of flowcharts in combination with data-extraction form were developed and tested the validity and consistency in a group of CCS with a known CEs. Chapter 5 we describe the incidence and risk factors of CEs after childhood cancer treatment in our complete Dutch cohort of 5-year childhood cancer survivors. Finally in chapter 6 we describe study design aspects of large pan-European cardiac cohort and nested case-control study.

The general aims of part 2 was to evaluate healthcare consumption and social outcomes among 5-year CCS.

In chapter 7 the aim was to quantify and compare hospitalization-related health problems in CCS and the reference population for specific chronic health conditions, and uncover (treatment related) risk factors. In chapter 8 the aim was to estimate the likelihood of not being married (or registered partner), not living independently and using social benefits compared to the general population and uncover risk factors for adverse social outcomes.

In chapter 9 the main study findings are described, strengths and weaknesses of the studies are discussed, conclusions are drawn and recommendations for future research are given.
References: