Cardiotoxicity in childhood cancer survivors

Risk of low dose cancer treatment,
added value of ECG in surveillance
and prevention by dexrazoxane

Esmée C. de Baat

Cardiotoxicity in childhood cancer survivors: risk of low dose cancer treatment, added value of ECG in surveillance and prevention by dexrazoxane

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Colophon

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The research described in this thesis was supported by a grant of the Dutch Heart Foundation (CVON2015-21).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

ISBN: 978-90-393-7583-9
Cover design: ©evelienjagtman.com
Layout: Publiss | www.publiss.nl
Printing: Ridderprint | www.ridderprint.nl

Cardiotoxicity in childhood cancer survivors: risk of low dose cancer treatment, added value of ECG in surveillance and prevention by dexrazoxane

Cardiotoxiciteit bij survivors van kinderkanker:
risico na lage doses kankerbehandeling, toegevoegde waarde van ECG bij surveillance en preventie door dexrazoxane

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

donderdag 12 oktober 2023 des middags te 2.15 uur

door

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geboren op 29 september 1994
te Raamsdonksveer

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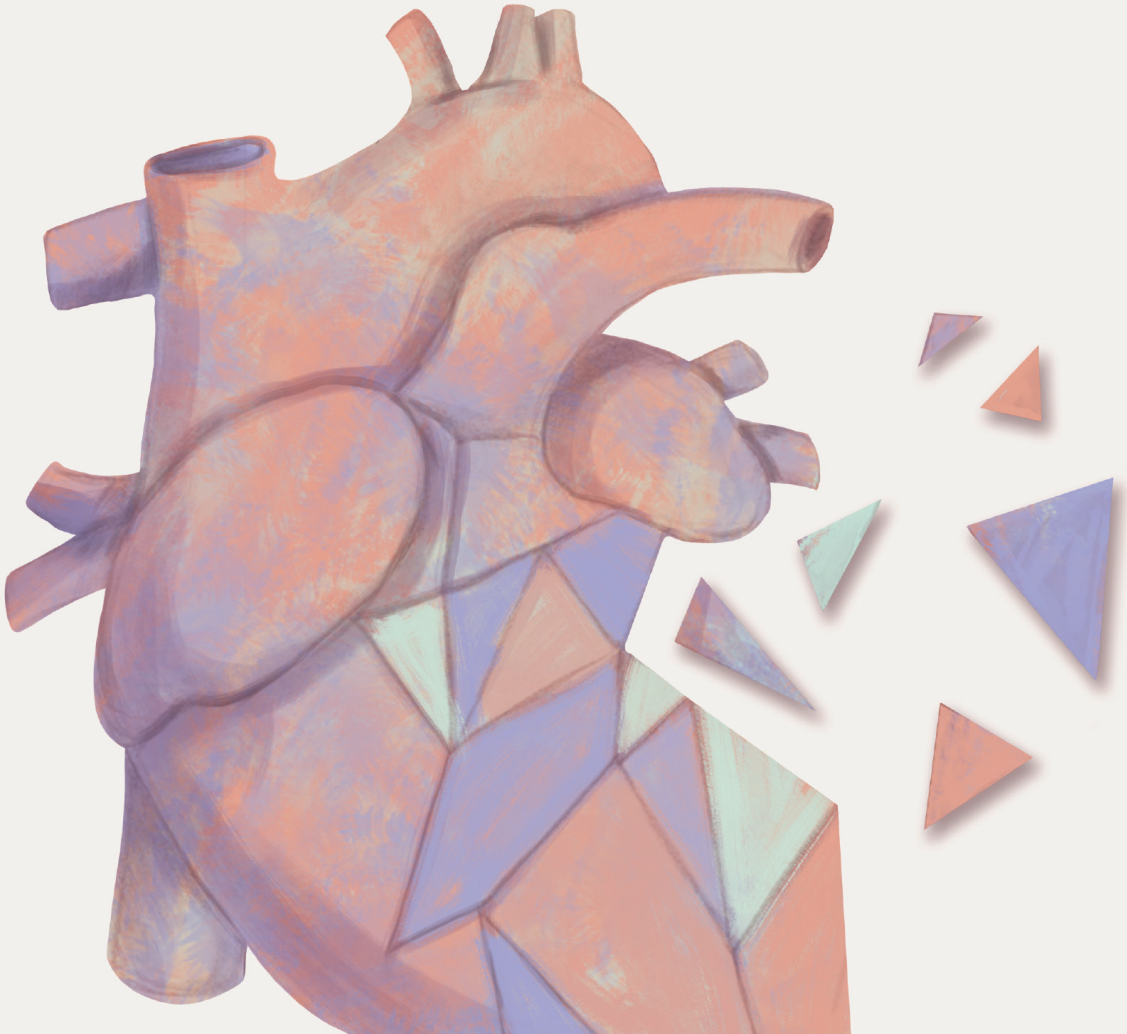

CHAPTER 1

Introduction and outline of the thesis

BACKGROUND

The survival of children with cancer has considerably increased over the last decades with 5-year survival rates currently exceeding 80%[1]. However, the excess burden of disease in the growing population of childhood cancer survivors (hereafter 'survivor' or 'CCS') are of major concern[2]. Cardiac diseases are one of the most frequent and severe long-term health effect, consequently the field of cardio-oncology has substantially evolved.

Cardiac diseases that can occur are subclinical myocardial dysfunction which can progress to clinical heart failure, coronary artery disease, valvular disease, pericarditis and arrhythmias[3]. In two previous Dutch cohorts of CCS who received cardiotoxic cancer treatment, van der Pal et al. reported subclinical cardiac dysfunction in 27% after a median follow-up period of 15 years[4] and Feijen et al. found a cumulative heart failure incidence of 10.6% 40 years after childhood cancer diagnosis[5]. The Childhood Cancer Survivor Study investigated the occurrence of cardiac events (defined by the Common Terminology for Criteria Adverse Events as grade 3 to 5) with questionnaires. They reported a cumulative incidence by 45 years of age of 4.8% for heart failure, 5.3% for coronary artery disease, 1.5% for valvular disease and 1.3% for arrhythmia[6].

Survivors are six-times more likely to have a cardiac disease compared to their siblings[7]. It also appears that survivors are more likely to be confronted with cardiovascular risk factors such as hypertension and dyslipidemia[8]. Cardiac diseases not only lead to increased morbidity, it also has a negative influence on the life expectancy of the survivors. A large study from Great Britain showed that the risk of death from cardiac causes is three-times greater for 5-year survivors compared to the general population[9].

Cardiac diseases develop as result of multiple factors with cancer treatment as the main contributor. Anthracyclines, mitoxantrone and radiotherapy (RT) including the heart region are well-established risk factors of myocardial dysfunction[3,5,10-15]. A recent study of Feijen et al. suggested cyclophosphamide as novel treatment-related risk factor[5]. Also, other risk factors have been proposed such as sex, age at cancer diagnosis, presence of traditional cardio-vascular risk factors and genetic susceptibility[7,15-19]. This thesis will mainly focus on risk prediction, early detection and primary prevention of cardiomyopathy defined as subclinical myocardial dysfunction and heart failure.

Cardiomyopathy

The European Society of Cardiology defines cardiomyopathy as "A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality"[20]. Cardiomyopathies can be divided into the following groups which are based on morphology and phenotype: hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, restrictive cardiomyopathy or unclassified (i.e., left ventricular non-compaction). Each cardiomyopathy type has different (non-)familial causes and toxins including anthracyclines and radiotherapy involving the heart region are associated with dilated cardiomyopathy[20,21]. Dilated cardiomyopathy is characterized by left ventricular dilation and systolic dysfunction which cannot be explained by hemodynamic changes or ischemia. The course of dilated cardiomyopathy is progressive, and the main goal of therapeutic intervention is reverse remodeling. Echocardiography is the cornerstone for the evaluation of left ventricular remodeling. The latent and early phase comprise changes in myocardial deformation (measured by speckle tracking) or diffuse fibrosis. Over time, the left ventricular volume will increase, and the left ventricular ejection will decrease which is associated with symptoms and poor prognosis[20-22].

Anthracycline-induced cardiomyopathy

Anthracyclines are important chemotherapeutic agents for the treatment of childhood cancers (i.e., acute lymphoblastic leukemia, sarcoma and Wilms-tumor) and are incorporated in more than 50% of the treatment protocols for pediatric cancers. The anthracycline analogues that have been associated with cardiotoxicity include doxorubicin, daunorubicin, idarubicin and epirubicin. Mitoxantrone, which is officially an anthraquinone, is often incorporated in the calculation of the cumulative anthracycline dose.

One of the ways by which anthracyclines prevent cell proliferation is interference with the enzyme topoisomerase II (Top2). It is proposed that Top2α, which is overexpressed in rapidly proliferating cells, has an important role in diminishing the tumor, while Top2β, which is expressed in quiescent cells such as myocardial tissue, is related to toxicity[23].

The mechanisms of anthracycline-induced cardiomyopathy are not fully understood yet. The main indicated mechanisms are redox cycling and inhibition of Top2β. First it was thought that doxorubicin generates free radicals and reactive oxygen species by linking their quinone ring with enzymes which lead to cellular oxidative stress and subsequent

DNA-damage, apoptosis and cardiac remodeling. More recent studies indicated that inhibition of the enzyme Top2β mediates doxorubicin-induced cardiomyopathy. The interaction between anthracyclines and Top2β prevents repair of breaks in DNA. It is postulated that these DNA changes lead to p53 mediated apoptosis and affect mitochondrial biogenesis. Mitochondrial dysfunction induces apoptosis and cardiac remodeling via processes such as inflammation and disturbance of Ca^{+2} homeostasis[23,24]. A key factor of cardiac remodeling after anthracycline treatment is an increase in interstitial myocardial fibrosis[24]. Imaging by magnetic resonance imaging enables visualization and characterization of myocardial tissue and interstitial fibrosis after anthracyclines is likely to be diffuse[25-28]. As mentioned before, mitoxantrone is often referred to as an anthracycline analogue. However, studies imply that the underlying pathology of mitoxantrone-induced cardiomyopathy differs from doxorubicin[29]. Interestingly, the cardiotoxic potential of mitoxantrone appeared 10-times higher when compared to doxorubicin which enhances the suggestion of a different pathophysiology[10].

The above-mentioned effects of anthracyclines and mitoxantrone are mainly associated with development of myocardial dysfunction which can progress to heart failure. In survivors who received anthracyclines with or without RT involving the heart region, the prevalence of subclinical myocardial dysfunction ranges from 0.3 to 30% at a median follow-up time of >9 years[30]. The risk of myocardial dysfunction increases with higher cumulative doses. There is no evidence of an increased risk for heart failure when survivors are treated with <100mg/m^2 [12,15,17]. Higher doses are associated with a significantly increased risk of clinical heart failure. Survivors who are treated with >250 mg/m^2 have a 5- to 10- times higher risk for heart failure when compared to survivors who did not receive anthracyclines [3,7,12,13,17]. On group level there is a clear association between the cumulative anthracycline dose and the risk of myocardial dysfunction, however variation exists in the occurrence of myocardial dysfunction between survivors who received similar doses. Recently, studies have suggested that genetic susceptibility to anthracycline-induced cardiomyopathy could explain a part of the differences in risk. The proposed genetic variations involve drug biotransformation, Top2β-mediated DNA damage, oxidative stress and iron metabolism[31-33]. These genetic variations could form an important base for individual risk-prediction.

In order to lower the effect of anthracyclines on the heart, multiple studies evaluated the effectiveness of primary prevention strategies. The identified options include altering the tissue distribution as with liposomal anthracyclines and the use of a longer anthracycline infusion duration. There are also cardio-protective pharmacologic interventions, of which

dexrazoxane is one of the most widely investigated. It is assumed that dexrazoxane decreases heart damage by chelation of iron, resulting in less the free radical formatin[34]. Furthermore, animal studies suggested that dexrazoxane may prevent heart damage via inhibition of Top2β [35,36]. Studies provided evidence that dexrazoxane prevents myocardial dysfunction[37]. However, dexrazoxane is not routinely used in clinical practice for children treated with anthracyclines. In 2017, the European Medicine Agency stated that dexrazoxane in contra-indicated for children up to 18 years receiving low cumulative anthracycline doses (<300 mg/m2 of doxorubicin or equivalent)[38]. This might be explained by a concern over interference with antitumor efficacy and the occurrence of secondary malignancies[39].

Radiation-induced cardiomyopathy

Radiotherapy is an important aspect of childhood cancer treatment and is used for several childhood cancer types (i.e. nervous system tumor, lymphoma, neuroblastoma and Wilms-tumor). Other indications for radiotherapy are pre-transplant conditioning for acute myeloid leukemia and reduction of pain or mass in the palliative setting. Besides treating the tumor, radiotherapy damages surrounding healthy tissue which can results in long-term sides effects. The manifestation depends on which part of the body was exposed to radiotherapy, the total dose, fractionating and volume of the irradiated tissue. Especially children are susceptible for the effects of radiotherapy because their organs are still developing. Examples of radiotherapy related side effects in survivors are secondary malignant tumors, endocrine related disorders and pulmonary and cardiac diseases[40]. Developments in radiotherapy techniques aimed to lower the side effects by addressing the above-mentioned factors. In the beginning, radiotherapy was robust and exposed the adjacent tissue to the same dose as the tumor. Once tomography (CT) was implemented, it became possible to plan the treatment more and more precisely. Also, improvements in beam arrangements decreased the given dose to healthy tissue. Over the past years the use of intensity-modulated radiation therapy has replaced 3-dimensional conformal radiation therapy for a large part. This technique can deliver higher doses to the tumor but exposes larger volumes of the surrounding tissue to low and moderate doses[41,42].

Formation of fibrosis is the main effect of radiotherapy that causes myocardial dysfunction[43]. Myocardial remodeling is a result of many different pathways. In the acute phase radiation incudes an inflammatory state including vasodilatation and increased vascular permeability which eventually triggers pro-fibrotic cytokines. In parallel, the

effects on fibroblasts lead to chronic deposition of collagen. Also, the oxidative stress and DNA damage will eventually lead to development of interstitial myocardial fibrosis. Cardiac remodeling induced by radiotherapy is a slow and progressive process and it takes years before there are signs of myocardial dysfunction[44,45].

As with anthracyclines, the prevalence of heart failure increases with higher doses of radiotherapy involving the heart region. Bates et al. demonstrated that after 30 years of follow-up, the cumulative incidence of heart failure is 1.4 for survivors who received a mean cardiac dose of 0.1-10 Gray and goes up to 6.9 for survivors who received a mean cardiac dose of ≥30 Gray[13]. Multiple studies have demonstrated that survivors who are exposed to moderate to high doses of radiotherapy involving the heart region are at risk of heart failure. Up to now, it is difficult to establish the risk of heart failure after low to moderate doses as studies uses different cut-off values with varying results[3,5,7,12-14,17,46].

Surveillance strategies and management

In 2015, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) developed a guideline for cardiomyopathy surveillance in 5-year survivors. They formulated recommendations for survivors who received anthracyclines and/or chest-directed radiotherapy. However, they were unable to formulate strong recommendations for the moderate and lower risk groups due to the quality of the evidence.

Echocardiography is the cornerstone cardiomyopathy surveillance as it enables assessment of the myocardial function and dimensions, the valves and pericardium. The myocardial function is reflected by the left ventricular ejection fraction, however this is relatively robust and late marker of myocardial dysfunction. Consequently, there is increasing interest in early and subtle measures of myocardial impairment such as global longitudinal strain. Other modalities that could play a role in early detection of myocardial damage are electrocardiography (ECG), blood biomarkers and cardiac magnetic resonance imaging.

One international follow-up guideline for survivors recommends to obtain a baseline ECG during the first visit (5 years after cancer diagnosis) at the long-term follow-up clinic and thereafter when clinically indicated[47]. While, population studies suggest that ECG abnormalities are associated with concurrent or future (cardiac) events[48-52] and might aid in ruling-out heart failure[53], there is no consensus on the use of this widely available tool in long-term survivors[54,55]. It is important to systematically assess ECG abnormalities in survivors, because it might optimize the surveillance guideline for cardiomyopathy.

Clear evidence on the initiation of heart failure therapy in survivors is lacking. Currently, the general (pediatric) heart failure guidelines are used for further investigation and management[53,56-58]. In addition, it is important to pay attention to a healthy lifestyle. Some survivors are more likely to develop cardiovascular risk factors such as hypertension, dyslipidemia and obesity due to the cancer treatment[59-61]. It has been demonstrated that independent of cardiotoxic cancer treatment, presence of these factors increases the risk of myocardial dysfunction[6,62]. However, the effectiveness of lifestyle interventions on cardiovascular risk factors or cardiovascular disease has not been established in survivors.

GENERAL DESIGN

The studies presented in this thesis were embedded in a cohort study, the Dutch Childhood Cancer Survivor Study, LATER cohort part 2 (DCCSS LATER 2), and international collaboration projects.

DCCSS LATER 2

The DCCSS LATER 2 is a multicenter cohort study in the Netherlands, including survivors ≥5-years after cancer diagnosis. The study is designed to evaluate the adverse effects of childhood cancer and its treatment that may occur many years after diagnosis. Examples of adverse effects other than cardiotoxicity that were addressed are infertility, secondary malignancies, pulmonary toxicity and psychosocial problems. More than 6,000 survivors were invited along with 278 siblings to serve as a control group for the cardiac study. All survivors who were diagnosed with childhood cancer before the age of 18 years and between 1/1/1963 and 12/31/2001 were eligible. Participants visited the outpatient clinic between February 2016 and February 2020 for questionnaires, physical examination, blood sampling, and additional tests (i.e., cardiac examination, spirometry, DEXA-scan). The set of additional tests was different for every survivor as it depended on the treatment exposed. The data center of the DCCSS LATER 2 collected and stored the information of the survivor and cancer treatment.

PanCareSurFup & ProCardio

The PanCarSurFup (PCSF) collaboration was initiated to pool the data of multiple European cancer registries and clinical centers. They aimed to investigate the incidence and risk factors of second cancers, cardiac diseases and late mortality. The evidence acquired through these studies will improve evidence based clinical practice guidelines for long-

term follow-up and eventually the quality of life of survivors. Another collaboration, ProCardio, was set-up to expand the projects investigating cardiac diseases. The cohort included survivors from seven European countries (France, Hungary, Italy, the Netherlands, Slovenia, Switzerland, and the United Kingdom (UK)). A survivor needed to be diagnosed <20 years of age with any type of childhood cancer between 1940 and 2009 and at least 5-years after cancer diagnosis. Eventually the cohort comprised more than 50.000 survivors and each country collected information of the survivor, cancer, treatment modalities and the occurrence of cardiac events. A cardiac event was defined as grade ≥3 according to the Criteria for Adverse Events. For the case-control study that was derived from this cohort, detailed information on the exposed treatment and cardiovascular risk factors was collected through medical records and questionnaires. The Institut Goustave Rousy performed radiotherapy organ dose reconstruction.

International Harmonization Guideline Group for Late Effects of Childhood Cancer

The IGHG is a worldwide effort to collaborate in guideline development. The IGHG created a handbook which is based on evidence-based methodology and facilitates systematic and transparent formulation of recommendations. The aim of the IGHG is to establish global consensus on the surveillance strategy of long-term effects in survivors in order to improve their quality of life.

OBJECTIVES

The major aims of this thesis are:

1. To assess whether low doses of cardiotoxic treatment are risk factors of heart failure.
2. To establish the prevalence of ECG abnormalities in survivors.
3. To assess the diagnostic value of ECG examination in cardiomyopathy surveillance of survivors.
4. To develop an international guideline for the administration of dexrazoxane in children who are expected to receive anthracyclines.

Outline of this thesis

The aim of the research described in this thesis is to improve the cardiac care of survivors by addressing treatment-related risk factors, early detection and primary cardioprotection. Other important topics in the field of cardio-oncology in children are also covered by the state-of-the-art review in **Chapter 2**.

It is important to investigate which survivors are at risk of cardiomyopathy to establish who needs surveillance. To get more insight in the effect of low doses of cardiotoxic cancer treatment, **Chapter 3** describes a Pan-European cohort and case-control study on heart failure. With the cohort study we investigate the cumulative incidence of heart failure and the differences in cumulative incidence between treatment periods. With the case-control study we investigated treatment-related risk factors of heart failure by multivariate conditional logistic regression and dose-response curves.

To improve early detection of cardiomyopathy, we explored the role of ECG examination in **Chapter 4**. First, we performed a systematic review to explore the available evidence on the prevalence and risk factors of ECG abnormalities in survivors who were treated with cardiotoxic treatment. This provides an important starting point for our large cohort study. The aim of this cross-sectional study was to assess the prevalence of ECG abnormalities according to the Minnesota Code, to identify ECG abnormalities that are associated with left ventricular dysfunction and to evaluate their potential added diagnostic value in cardiomyopathy surveillance.

Chapter 5 describes two parallel and complementary efforts on the use of dexrazoxane during cancer treatment. We updated a Cochrane systematic review and meta-analysis on the efficacy and safety of dexrazoxane in children and adults. In addition, a working group within the IGHG developed a guideline about the administration of dexrazoxane in children that will receive anthracycline as part of their cancer treatment.

In **Chapter 6** the main findings of all studies are discussed, and future perspectives are presented. It also covers a Dutch summary of the research presented in this thesis. **The appendices** present the acknowledgements, curriculum vitae and list of publications.

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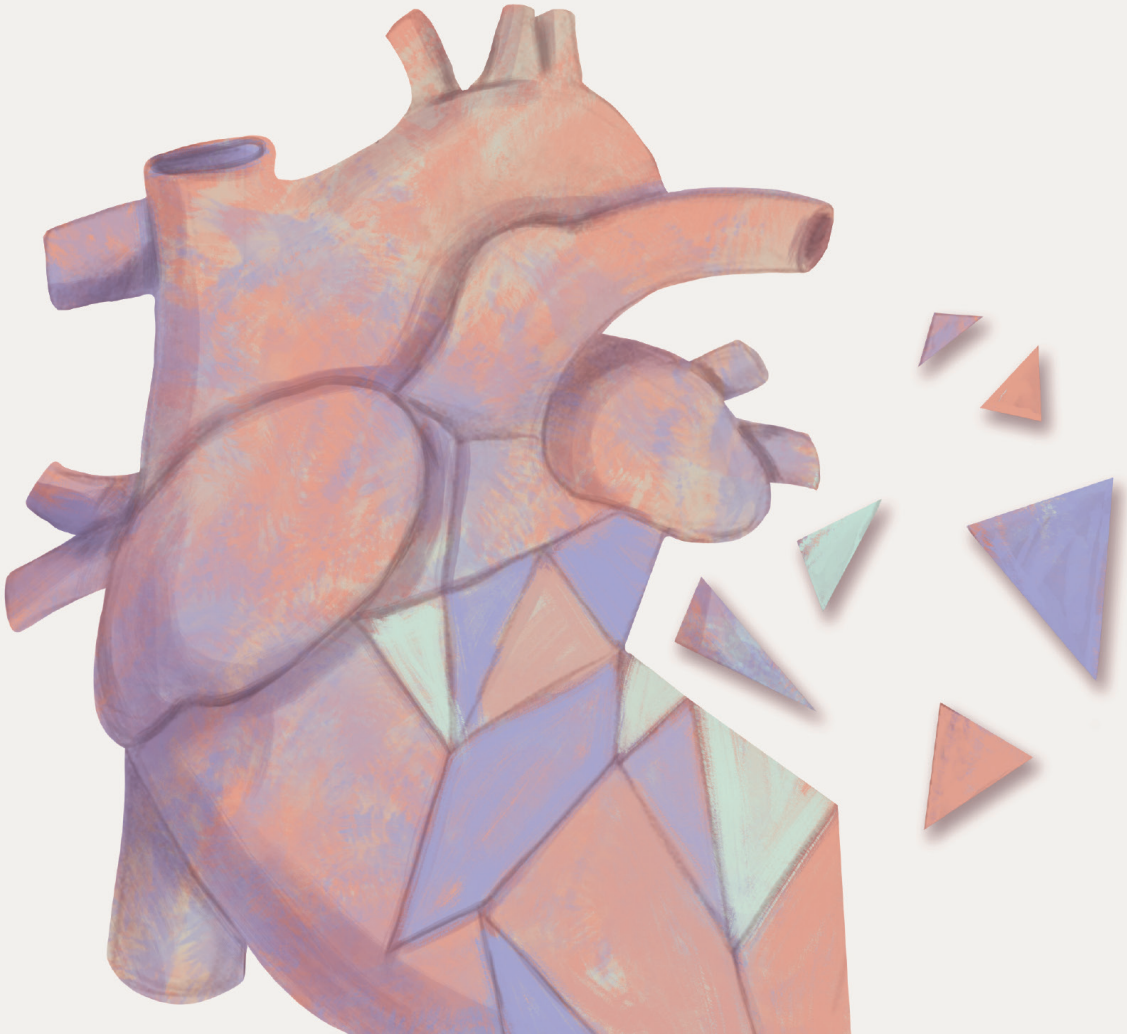

CHAPTER 2

Cardiac disease in childhood cancer survivors: risk prediction, prevention, and surveillance. *State-of-the-Art review*

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Journal of the American College of Cardiology:
CardioOncology. 2020 Sep 15;2(3):363-378

ABSTRACT

Cardiac diseases in the growing population of childhood cancer survivors are of major concern. Cardiotoxicity as a consequence of anthracyclines, and chest radiotherapy continues to be relevant in the modern treatment era. Mitoxantrone has emerged as an important treatment-related risk factor and evidence on traditional cardiovascular risk factors in childhood cancer survivors is accumulating. International surveillance guidelines have been developed with the aim to detect and manage cardiac diseases early and prevent symptomatic disease. There is growing interest in risk prediction models to individualize prevention and surveillance. This State-of-the-Art review summarizes literature from a systematic PubMed search focused on cardiac diseases after treatment for childhood cancer. Here, we discuss the prevalence, risk factors, prevention, risk prediction, and surveillance of cardiac diseases in survivors of childhood cancer.

INTRODUCTION

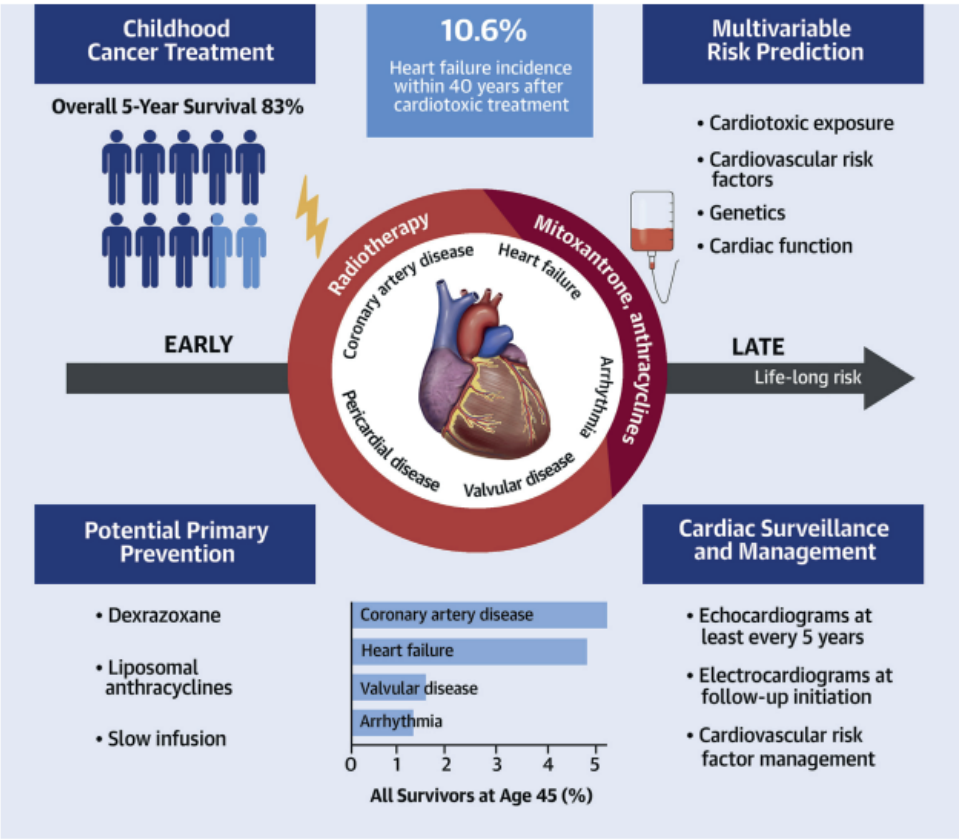
The survival of children with cancer has considerably increased over the last decades with five-year survival rates currently exceeding 80% (1). However, the long-term health effects in the growing population of childhood cancer survivors (CCS) are of major concern (2). Cardiac disease, as a consequence of treatment with anthracyclines, mitoxantrone and/or chest-directed radiotherapy (chest RT), can manifest as myocardial dysfunction and heart failure but also as valvular disease, coronary artery disease, arrhythmias and pericardial disease, depending on the exact cardiotoxic agent (3).

In this state-of-the-art review, we focus on long-term cardiac diseases after treatment for childhood cancer. We discuss the prevalence, risk factors, prevention, prediction and surveillance of cardiac disease in this population (Central Illustration). We systematically searched PubMed for studies that described cardiac adverse events in children treated with cardiotoxic cancer treatments. We limited the search to full-text articles written in English and articles published within the last 10 years. We selected articles with a study cohort of which >50% were treated for childhood cancer before the age of 21. For studies describing the prevalence or cumulative incidence of heart failure, we reviewed articles with a minimum of 500 CCS; a minimum of 100 CCS was required for the other outcomes. Studies on primary prevention strategies were identified from previous Cochrane searches (4-6). Based on these criteria, 74 studies were considered to be described in this review (Figure 1). The full search strategy is provided in the Supplemental Appendix.

CARDIAC DISEASES AND TREATMENT-RELATED RISK FACTORS IN CHILDHOOD CANCER SURVIVORS

Heart failure

Multiple studies have demonstrated that left ventricular (LV) systolic function deteriorates as a result of cardiotoxic treatment (7-15). Anthracyclines are clearly associated with cardiomyocyte damage. Although the exact mechanism of anthracycline-induced cardiotoxicity has not been fully elucidated, early studies point to cardiotoxicity through reduction–oxidation reaction cycling and the generation of reactive oxygen species. More recently, topoisomerase 2β has been proposed to be a mediator of doxorubicin-induced cardiac injury (16).



Central illustration Overview of Clinical Practice in Childhood Cancer Survivors at Risk for Cardiotoxicity.

The prevalence of cardiac diseases, risk prediction models, preventive measures, and surveillance recommendations are illustrated based on available evidence and promising research topics of cardiotoxicity in childhood cancer survivors. Numbers derived from Siegel et al., 2019 (122); Feijen et al., 2019 (10); and Armstrong et al., 2013 (17).

Systolic dysfunction can eventually progress to heart failure. Heart failure is one of the most frequent cardiac late effects in CCS (17,18), and contributes to significant morbidity and non-cancer related mortality later in life (19,20). A large cohort from the Childhood Cancer Survivor Study investigated the occurrence of heart failure, defined by the Common Terminology for Criteria Adverse Events grade 3-5. Based on questionnaires in long term CCS, the reported cumulative incidence is 4.8% by 45 years of age (17). These results confirmed earlier reports that anthracyclines and chest RT are strongly associated with heart failure (21). Recently, it has been demonstrated that even low-to-moderate chest RT doses increase the risk of heart failure substantially (22,23). In the Dutch LATER

cohort, Feijen et al. reported a cumulative heart failure incidence of 10.6%, 40 years after childhood cancer diagnosis in CCS that received cardiotoxic cancer treatment. Interestingly, higher exposure to mitoxantrone and cyclophosphamide were suggested as novel treatment-related risk factors (10). While mitoxantrone has traditionally been classified as an anthracycline, it has been suggested that mitoxantrone results in cardiotoxicity through mechanisms different from anthracyclines (24,25). Mitoxantrone has a non-linear dose-response relationship with heart failure risk (10,26-28), and compared to doxorubicin, mitoxantrone is 10-times more cardiotoxic. In addition, a younger age at diagnosis and presence of traditional cardiovascular risk factors may play a role in the development of heart failure (29). The influence of sex on the development of myocardial dysfunction is still incompletely conclusive (8,9,11,12,30).

Coronary artery disease

The risk of coronary artery disease is substantially increased in CCS. In the Childhood Cancer Survivor Study, the cumulative incidence of coronary artery disease by age 45 years was 5.3% in survivors with and without exposure to cardiotoxic cancer treatments (31). This risk is dependent on chest RT dose with no established safe dose; this risk is also higher in males. The cumulative incidence of symptomatic coronary artery disease at age 50 goes up to 20% in males exposed to >35Gy (18,32). The St. Jude Lifetime cohort study detected coronary artery disease, based on either history, electrocardiogram (ECG) or echocardiography in 3.8% of asymptomatic CCS 22.6 years after cardiotoxic therapy (30). However, evidence from (non)invasive coronary angiography is scarce. A study evaluating computed tomography in asymptomatic Hodgkin lymphoma CCS aged ≤55 years (n=31) exposed to chest RT showed coronary artery lesions to be very proximal, placing large portions of the myocardium at risk (33).

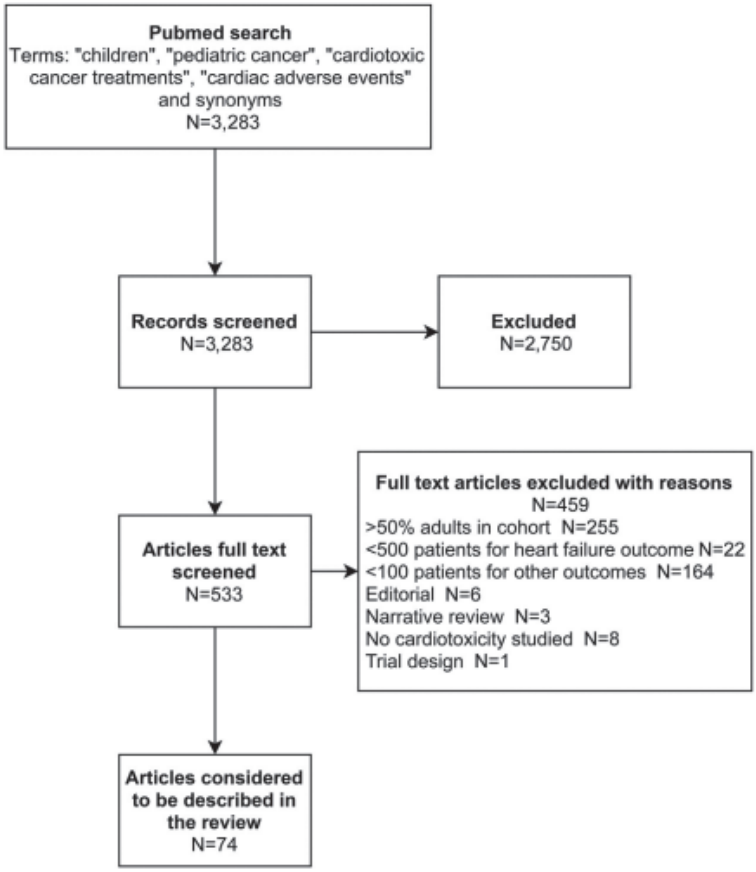


Figure 1 Flowchart of Study Inclusion.

Flowchart describing the systematic literature search in PubMed and the inclusion of relevant studies.

Valvular heart disease

Several studies have investigated valvular abnormalities in CCS (11,17,30,34-36), with a reported prevalence of up to 31% (30,34,36). Chest RT has been identified as an important risk factor that increases at higher doses (36). Other risk factors are treatment with anthracyclines, hypertension, congenital heart disease and younger age at diagnosis, although these have not been uniformly demonstrated in all studies (11,30,34). Mild tricuspid regurgitation was most prevalent in two studies describing valvular disease, but it is important to note that this is also very common in the general population (30,34,37). In lymphoma CCS who were exposed to chest RT, valvular heart disease, defined as mild

or higher for left sided valves and moderate or higher for right sided valves, was most frequently detected in the aortic and mitral valves (36). Valvular abnormalities after chest RT are most likely caused by direct irradiation injury to the valve cusps or leaflets, causing thickening, fibrosis, and calcification (30,38). These processes progress with age and increase in prevalence over time (30,36). Hence, CCS without echocardiographic abnormalities after a short follow-up period are still at risk of severe valvular heart disease.

Pericardial disease

Besides paraneoplastic and infectious causes, pericardial disease can arise from chest RT. Late constrictive pericarditis, in particular, can lead to disabling symptoms and a poor prognosis (39). However, data on pericardial disease in CCS are limited. The Childhood Cancer Survivor Study showed a 10-fold higher risk of pericardial disease in all CCS versus siblings (30-year cumulative incidence 3.0%) and a dose-response relation with chest RT (18). A single center study in CCS >5 years after diagnosis (n=1,362; 47% no cardiotoxic therapy), reported symptomatic pericarditis in only 2 CCS (18). Although the diagnosis of constrictive pericarditis is difficult by echocardiography, thickening of the pericardium as well as hemodynamic consequences (e.g. 'septal bounce', abnormal respiratory variations in Doppler findings) can be suggestive. Upon high clinical suspicion, cardiac computed tomography, magnetic resonance imaging (MRI) and/or invasive hemodynamic evaluation may be needed to confirm the diagnosis (40).

Arrhythmias

The prevalence of symptomatic cardiac arrhythmias in long term CCS is reportedly low (11,18,31,41). In 10,724 CCS, the cumulative incidence of grade 3 to 5 arrhythmia by 45 years of age was 1.3% (31). A subsequent study (n= 23,462) demonstrated that chest RT > 35 Gy, anthracycline dose ≥250 mg/m^2, dyslipidemia and hypertension are risk factors for symptomatic arrhythmia (11). Myocardial fibrosis caused by chest RT may contribute to the occurrence of arrhythmias. Other frequently used cancer agents for pediatric cancers such as cisplatin, cyclophosphamide and tyrosine kinase inhibitors may also be associated with supraventricular and ventricular arrhythmias (42,43). Prolonged QTc interval, which has arrhythmogenic potential, has been demonstrated in CCS that received anthracyclines or chest RT (44,45). Also, rhythm disturbances like premature ectopic beats and atrioventricular blocks have been reported in CCS (46-48). The literature on ECG abnormalities in large cohorts of long term CCS is sparse (47,48), data on the use

of ambulatory ECG monitoring to define the prevalence of brady- and tachyarrhythmias induced by cardiotoxic cancer treatments are needed, but needs to be carefully weighed against the burden and clinical relevance.

PREVENTION OF CARDIAC DISEASE IN CHILDHOOD CANCER SURVIVORS

Preventive measures for cancer treatment-induced cardiotoxicity

As the risk of cardiac disease is high in chest RT and anthracycline treated survivors and as omitting or diminishing the use of cardiotoxic treatments is not always possible, prevention is critical (49). Advanced radiotherapy techniques to minimize exposure to the heart have been developed; the impact of those improvements is reflected by the decrease in coronary artery disease in more recent treatment eras (11).

Extensive research has been devoted to the identification of possible cardioprotective interventions during anthracycline treatment that do not have negative effects on anti-tumor efficacy or other non-cardiac adverse effects. Below we discuss three preventive measures that have been studied during anthracycline treatment. We focus primarily on randomized controlled trials (RCTs), as they provide the highest level of evidence to answer this type of question. It should be kept in mind that due to developmental changes and the differences in the body composition of children, data from adults cannot be reliably extrapolated to children (50).

Dexrazoxane

Dexrazoxane is one of the most widely investigated cardioprotective pharmacological interventions. It has been shown in adult cancer patients to prevent clinical and subclinical cardiac damage (4). The few published pediatric RCTs have included participants diagnosed with leukemia, lymphoma and sarcoma (51-53). These studies suggest that there are no significant differences in clinical heart failure between dexrazoxane and control patients (4,54), although dexrazoxane might have a protective effect on asymptomatic cardiotoxicity (54,55). All studies included relatively short-term follow-up, and the impact on outcomes after longer follow-up is yet unknown.

Currently, dexrazoxane is not routinely used in clinical practice for all children treated with anthracyclines. This might be explained by a concern over interference with anti-

tumor efficacy and the occurrence of secondary malignancies (56). However, high quality evidence to support an increased risk of secondary malignancy is lacking. A Cochrane systematic review identified no significant differences between treatment groups (4), which is in line with more recently published randomized trials (51,54).

A recently published non-randomized study in pediatric patients with acute myeloid leukemia (n=1,014) added important knowledge about the efficacy and adverse effects of continuous use of dexrazoxane versus no dexrazoxane. Results demonstrated that after a median follow-up period of 3.5 years, cardiac function was preserved with dexrazoxane without negative influence on anti-tumor efficacy or non-cardiac toxicities. Importantly, the influence of possible differences in cumulative anthracycline dose per treatment group could not be evaluated in this study (57).

At the moment clear guidance on the use of dexrazoxane is missing. Since it will take many years to add relevant knowledge by new RCTs, additional observational studies are needed. The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) is currently preparing recommendations based on the existing evidence.

Liposomal anthracyclines

Another option is to limit drug exposure in healthy tissues such as the heart and increase drug activity in malignant cells by altering the tissue distribution, as with liposomal anthracyclines (58). Liposomal anthracyclines have shown promising results in adults with breast cancer (5). In a meta-analysis of two studies, liposomal-encapsulated doxorubicin significantly reduced both clinical and subclinical heart failure when compared to the same dose of conventional doxorubicin, without negative effects on antitumor-efficacy and without cardiac adverse effects. In one of the studies, patients received a higher cumulative anthracycline dose in the liposomal group. However, again follow-up was relatively short and we do not know how longer term follow-up will influence these results (5). One study compared liposomal-encapsulated doxorubicin to the same dose of conventional epirubicin. No significant difference in cardiotoxicity was shown, but that might have been the result of inadequate power or a limited follow-up period (5). To our knowledge, no pediatric RCTs have been performed, so the benefits and harms of liposomal anthracyclines in children remain unclear. High-quality research in children is needed before definitive conclusions can be made.

Infusion duration

The use of longer anthracycline infusion durations may play a role in primary prevention of cardiotoxicity. A Cochrane systematic review compared different anthracycline infusion durations in children and adults with cancer (6). An anthracycline infusion duration of six hours or longer seemed to reduce the risk of both clinical heart failure and subclinical cardiotoxicity. A clinical practice guideline for children treated with anthracyclines has suggested that although it was not possible to formulate a recommendation regarding a precise and optimal prolonged infusion duration, the use of an anthracycline infusion duration of at least one hour was strongly recommended (59). Since data in children is limited, different anthracycline infusion durations should be evaluated further in children.

Cardiovascular risk factors and healthy lifestyle

For both primary and secondary prevention of cardiovascular disease in CCS, management of cardiovascular risk factors and counseling on healthy lifestyle are essential, although most evidence is still derived from the general population.

Metabolic syndrome

Hypertension, obesity, dyslipidemia and diabetes, together clustered as metabolic syndrome, are well-known risk factors for cardiovascular disease (60). Some CCS are at increased risk to develop metabolic syndrome due to previous cancer treatment. Metabolic syndrome has been established in 9% of French childhood leukemia survivors and in 32% of the St. Jude Lifetime cohort, at median attained ages of 21 to 32 years (61,62). Survivors treated with cranial radiotherapy are at risk of developing metabolic syndrome, especially obesity (63). Furthermore, abdominal radiation and nephrotoxic treatment may result in the development of cardiovascular risk factors (64,65). Hypertension is the most prevalent cardiovascular risk factor in CCS, approaching 40% in survivors aged ≥50, versus 26% in siblings (17). The Childhood Cancer Survivor Study (n=10,724) investigated cardiovascular risk factors with longitudinal questionnaires and showed that hypertension had the strongest association with all cardiac events and mortality, compared to diabetes, dyslipidemia and obesity (17). In the St. Jude Lifetime study, hypertension was also the only cardiovascular risk factor associated with an abnormal LVEF (7).

Management of cardiovascular risk factors is essential in all CCS, and particularly in those at risk for cardiac disease. No studies have assessed whether more aggressive approaches and treatment goals than in the general population are beneficial in CCS

with a high lifetime risk of cardiovascular disease. Lifestyle interventions may prevent the occurrence of cardiovascular risk factors and cardiac disease and may complement pharmacological risk factor modification.

Healthy lifestyle

A healthy lifestyle, including cessation and abstinence from smoking, a sufficient level of physical activity, a healthy diet and less than moderate alcohol use, may benefit cardiovascular health. It may prevent the onset and/or reduce the severity of cardiovascular disease, directly, or indirectly by lowering the risk of metabolic syndrome (60). Although the association between lifestyle factors and cardiovascular disease has been well established in youth and aging adults (60), there are few studies that have examined the association between lifestyle and either cardiovascular disease or cardiovascular risk factors in CCS. In the Childhood Cancer Survivor Study, smoking was not associated with cardiac events, most likely due to short exposure time and follow-up (17). In the St. Jude Lifetime cohort study, CCS who did not meet most of the lifestyle recommendations from the World Cancer Research Fund/American Institute for Cancer Research, were more likely to have metabolic syndrome than CCS who did meet these recommendations (62). In recent studies in the St. Jude Lifetime cohort, CCS were shown to have substantially less exercise capacity than community controls on maximal cardiopulmonary fitness testing in recent studies. Exercise capacity was associated with all-cause mortality, cardiac function (global longitudinal strain [GLS], but not LVEF), chronotropic incompetence, and worse pulmonary and muscle function (66). Furthermore, CCS with lower exercise capacity had more emotional distress and worse attainment of social roles and health-related quality of life (67). Although causal relations have not been established, based on the above results in the general population and CCS, it is widely assumed that healthy lifestyle interventions will contribute to less cardiac morbidity and mortality. However, the effectiveness of lifestyle interventions on cardiovascular risk factors or cardiovascular disease has not been established in CCS.

Several studies have been performed to support CCS to adapt to a healthy lifestyle, of which most have focused on increasing physical activity. In a meta-analysis of nine studies, aerobic exercise was positively related to cardiopulmonary fitness in CCS (68). A systematic review by Raber et al. identified twelve studies on physical activity interventions in CCS. Of these, five studies found that exercise training improved strength, functional mobility and flexibility and/or anthropometric fitness (69). Another systematic review on lifestyle interventions in adolescent and young adult cancer survivors targeting one or more health behaviors identified twelve studies, of which six were successful in changing health behavior (70). Three

of these were focused on influencing multiple behaviors, including an individually tailored counseling program on smoking and alcohol consumption. Half of the reviewed studies delivered lifestyle interventions remotely, using phone calls or online contact. Personalized e-health interventions seem a relatively cost-effective and feasible way to improve lifestyle in CCS, but more studies are need to examine its efficacy and effectiveness.

RISK PREDICTION MODELS

Knowledge of the risk of cardiac adverse events before or early after cardiotoxic cancer treatments can be very useful to guide the care for CCS. Multivariable risk prediction models have the potential to accurately estimate risk in individual survivors and should ideally be linked to a proven effective action to prevent or reduce the severity of cardiotoxicity (71,72).

Development of prediction models broadly includes a development and validation phase (71). In the development phase, relevant predictors are selected based on subject knowledge and/or stepwise regression (73). Subsequently, model discrimination and calibration are assessed. Discrimination is the ability of the model to discriminate between patients who develop the event and those who do not and is typically quantified by the C-statistic or area under the receiver operating characteristic curve (73,74). Calibration refers to how well the predicted risks match the actual risks and can be assessed with a calibration plot (72). In the validation phase, discrimination and calibration are assessed in a distinct cohort, a critical step before the prediction model can be applied to patients (71,72). In CCS, risk prediction models have been developed for heart failure, ischemic heart disease and cardiovascular mortality. An overview of validated prediction models in CCS is provided in Supplemental Table 2.

Heart failure prediction models

Practical models to predict heart failure onset before the age of 40 years in CCS at 5-years after cancer diagnosis have been developed by Chow et al. (29). Here, prediction models in 13,060 CCS (285 with heart failure) from the Childhood Cancer Survivor Study were derived, and subsequently validated in 3,421 CCS (93 with heart failure) from the Dutch Emma Children's Hospital, the National Wilms Tumor Study and the St Jude Lifetime Cohort Study. Using a backward selection procedure, female sex, younger age at cancer diagnosis, anthracycline dose and chest RT dose were selected as predictors and assigned integer risk scores for clinical applicability. The final prediction model showed reasonable discrimination between CCS who developed heart failure and those

who did not (C-statistic: 0.76 and 0.68-0.82 in the development and validation cohorts, respectively). The discriminatory abilities of the model were further demonstrated by a cumulative incidence of heart failure at age 40 of 0.5% in the low-risk group, while this was 11.7% in the high-risk group. Importantly, 45.2% of the CCS were at low risk according to the model and thus unlikely to develop heart failure.

Ischemic heart disease prediction models

A similar approach was used by the same authors to develop and externally validate a prediction model for ischemic heart disease before age 50 years (32). Male sex and higher chest RT dose were selected as predictors. The Cox regression model achieved modest discrimination between CCS who developed ischemic heart disease and those who did not (C-statistic of 0.70 in the development cohort and 0.66 in the validation cohort). Cumulative incidences of ischemic heart disease at age 50 ranged from 2.3% (95% CI 1.5%-3.1%) in the low-risk group to 19.9% (95% CI 15.0%-24.7%) in the high-risk group, while this was only 1.2% (95% CI 0.4%-2.0%) in siblings. Although a clear segregation was observed between the low- and high-risk groups, the C-statistics were modest. Of note, for both the heart failure and ischemic heart disease prediction models, calibration was not assessed.

Traditional cardiovascular risk factors in the prediction for heart failure and ischemic heart disease

Modifiable cardiovascular risk factors in CCS are known to increase the risk for cardiovascular events and their prevalence is strongly related to age (17). Thus, early, at 5-years after diagnosis, cardiovascular risk factors have been shown to provide little incremental information to prediction models for heart failure and ischemic heart disease (29,32).

In a more recent study, diabetes, hypertension and dyslipidemia were used in the prediction of heart failure and ischemic heart disease in CCS aged 20, 25, 30 or 35 years at time of prediction, with relative risks comparable to moderate doses of anthracyclines (75). Cardiovascular risk factors were present in approximately 10% of the CCS at age 35 and were strong predictors of heart failure and ischemic heart disease. Although the discrimination of the prediction models improved with the addition of cardiovascular risk factors, the C-statistics were modest for both events ranging from 0.69-0.79 in the derivation cohort with successful replication in the other half of the cohort. Of importance, both the heart failure and the ischemic heart disease predictions models showed good calibration. A small, very high-risk group was identified with cumulative incidences of heart failure or ischemic

heart disease of ~10% at age 50 years; survivors in this high-risk group may benefit from more frequent surveillance and/or early interventions to modify their risk. However, low risk survivors that may be excluded from further surveillance could not be identified with these models as cumulative incidences of heart failure (~1.5-2.5%) and ischemic heart disease (~1-1.5%) were still significantly higher compared to siblings at age 50 years.

Cardiovascular mortality prediction models

A population-based study from the Surveillance, Epidemiology, and End Results Program in 28,811 CCS was used to develop and validate a clinical risk score for cardiovascular mortality ≥5 years after diagnosis (76). Male sex, non-white race, age at diagnosis, lymphoma history and any radiation were selected as predictors in the Cox regression model. This simple model showed modest discrimination (C-statistic 0.72-0.75) and good separation between low-risk and high-risk survivors (cumulative incidence at 30 years after cancer diagnosis of 0.7% and 6.0%, respectively).

Genetic risk prediction models

There is large inter-individual variation in the susceptibility for cardiotoxicity after anthracycline treatment (78). Genetic predisposition may explain why some children will develop cardiotoxicity at lower anthracycline doses while others who are treated with high doses will not, and thus enable risk stratification of children before anthracycline treatment. Several genetic variants implicated in DNA damage, oxidative stress, iron metabolism, sarcomere dysfunction, anthracycline metabolism and transport have been described and replicated in anthracycline cardiomyopathy (Figure 2, Supplemental Table 3) (77-79). For a comprehensive overview of genetic variants implicated in anthracycline cardiomyopathy we refer the reader to an upcoming state-of-the-art review in this journal and other systematic reviews (77,78).

In the absence of single genes explaining the susceptibility for anthracycline cardiomyopathy, combining genetic and clinical risk factors in a multivariable prediction model may increase the clinical usefulness of screening for genetic variants. Visscher et al. developed several genetic risk prediction models. Validation of the first prediction model failed in an independent cohort (80,81). An updated prediction model based on 7 genetic variants and the clinical variables age at start of treatment, anthracycline dose, sex, chest RT and ethnicity, achieved an area under the curve (AUC) of 0.79 (95% CI 0.74-0.85) in the derivation cohort and 0.76 (0.68-0.83) in the validation cohort, compared to 0.68 (0.61-

0.75) for the model with clinical variables only (82). While these are promising results, this genetic risk prediction model is not ready to be applied to clinical practice due to several limitations. Calibration was not performed and coefficients of the final model were not provided. In addition, a logistic regression model was used that does not take into account the time-to-event, and also does not properly address survivors who dropped out before the study was performed. Therefore, the model estimates the probability of developing anthracycline cardiomyopathy at *any* time during follow-up, while it is likely more informative for clinician to understand the probabilities within a certain timeframe. Studies that evaluate the predictive value of genetic variants in combination with clinical variables using time to event analyses are needed before genetics can be used in the risk stratification for anthracycline cardiomyopathy in CCS.

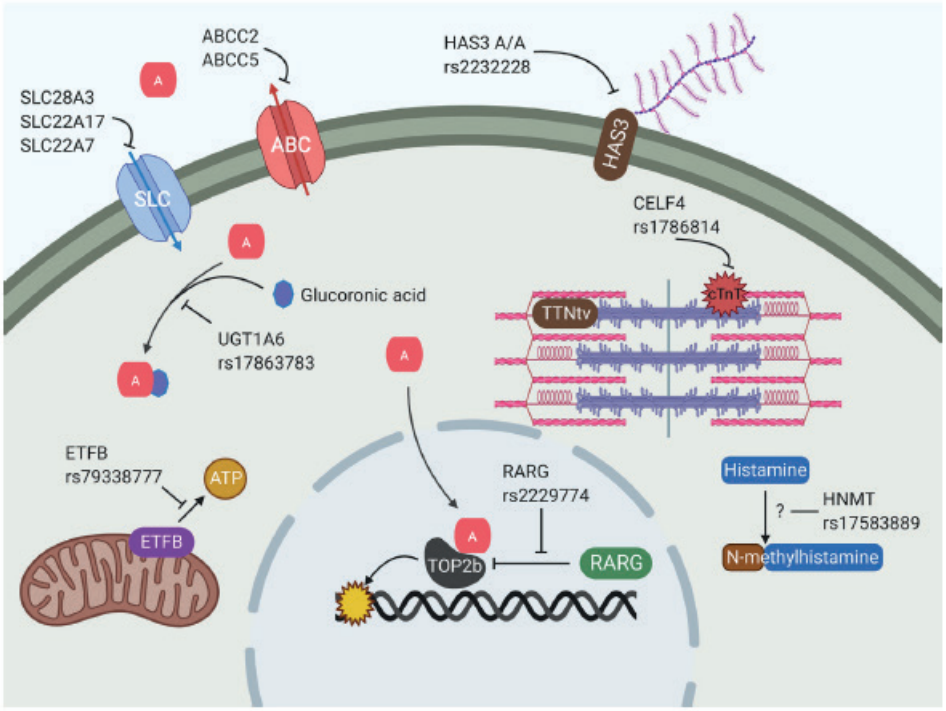


Figure 2 Replicated Genetic Variants Associated With Anthracycline-Induced Cardiomyopathy in Childhood Cancer Survivors and Their Cellular Functions**.**

Created with BioRender.com. A=anthracyclines; ABC=adenosine triphosphate binding cassette; ATP=adenosine triphosphate; CELF4=CUGBP Elav-like family member 4; cTnT=cardiac troponin T; ETFB=electron transfer flavoprotein subunit beta; HAS3=hyaluronan synthase 3; HNMT=histamine N-methyltransferase; RARG=retinoic acid receptor gamma; rs=reference single nucleotide polymorphism identification; SLC=solute carrier transporter; TOP2b=topoisomerase2b, TTNtv=titin truncating variant; UGT1A6=UDP glucuronosyltransferase family 1 member A6.

Improving prediction models with additional predictors

Improvements in discrimination ability of the models may be achieved with the addition of echocardiographic parameters, ECG, blood biomarkers and/or genetic variants (7,48,83). Updating risk estimates in a particular survivor with changes in echocardiographic, ECG and/or blood biomarkers during follow-up may also improve predictions given the results in other areas of research (84). Moreover, acute or early-onset cardiotoxicity is suggested as a predictor for late-onset cardiotoxicity (85).

Clinical applications and clinical impact analyses of prediction models

When a potentially high-risk patient is identified by a risk prediction model, preventive measures such as the use of dexrazoxane or liposomal anthracyclines may be considered. Prediction models using covariates that are known before cancer treatment, such as genetic variants or treatment protocols, may be useful for this purpose.

As a future application of prediction models, the predicted risk for cardiotoxicity can be weighed against the survival benefit associated with a particular treatment to guide therapy decisions. Risk estimates from a prediction model can also be used to individualize surveillance for asymptomatic cardiac dysfunction in CCS. Closer follow-up can be recommended in high-risk patients while at the same time the surveillance burden can be decreased in patients at low risk for cardiotoxicity.

While the above-mentioned prediction models may be used to inform survivors and clinicians on individual risks for cardiotoxic events, there is a lack of evidence-based clinical actions that can be taken based on the risk estimates from current models. This underlines the need for clinical impact analyses to investigate changes in clinical management linked to the results from a prediction model. A trial with a cluster randomization design evaluating usual survivorship care compared to care based on results from a prediction model will provide the strongest evidence but may be impractical to perform in CCS due to the long follow-up needed (86).

Another approach to assess clinical impact is decision modeling (86,87). Decision curves can evaluate the net benefit of a prediction model across a range of disease probability thresholds for intervention (88). In the context of prediction model guided surveillance this can be seen as the benefit of early detection of asymptomatic cardiac dysfunction among those who will develop heart failure (true positives) weighted against the potential

harm of an unnecessary diagnostic workup and/or treatment in those who will not develop heart failure (false positives).

Through decision modeling using simulations, it has been shown that routine echocardiographic surveillance for asymptomatic cardiomyopathy every 10 years may be more cost-effective, especially in those treated with an anthracycline dose <250 mg/m^2 (87). Decision modeling provides weaker evidence on the clinical impact compared to an RCT, but requires no follow-up and is less expensive to perform. Such analyses could be performed to assess clinical impact and cost-effectiveness before conducting an RCT.

DETECTION METHODS AND GUIDELINES

In order to detect anthracycline-cancer treatment induced cardiomyopathy there are different methods and techniques available. Much of the research in detection of cardiac diseases is focused on improving early detection of myocardial dysfunction. We will describe diagnostic methods that have been studied over the past decade in CCS.

Conventional echocardiography

Echocardiographic measurement of the shortening fraction (FS) and biplane left ventricular ejection fraction (LVEF) are widely used techniques to quantify cardiac dysfunction in survivors of childhood cancer. Fractional shortening is discouraged in patients secondary to potential regional wall motion abnormalities (89). Moreover, LVEF and FS decreases may reflect later stages of cardiotoxicity. To overcome these limitations, developments in advanced imaging techniques are of great importance. Application of three-dimensional echocardiography has improved inter- and intra-observer variability, which is desirable for longitudinal follow-up (90). Armstrong et al. demonstrated that the sensitivity and false-negative rate of three-dimensional echocardiography for detection of LVEF<50% measured by cardiac MRI as the gold standard, was improved compared to two-dimensional echocardiography (91).

Strain imaging and diastolic function

One of the markers that may detect myocardial dysfunction at an early stage is GLS. In adult cancer patients strain imaging has potential to predict subsequent LVEF deterioration (92,93). A relative GLS decrease of >15% from baseline is suggested as potentially abnormal, whereas a relative decrease of <8% seems not clinically relevant (94). Evidence on strain imaging in CCS is accumulating. Mavinkurve-Groothuis et al.

showed a significant difference in GLS between asymptomatic CCS (n=111) approximately 15 years after anthracycline treatment and healthy controls (95). A large study of the St. Jude Lifetime cohort of 1,807 CCS over a median follow-up of 23 years determined an abnormal GLS in 28% of the cohort who were exposed to anthracyclines and/or chest RT who had a normal LVEF. Both cumulative anthracycline dose >300 mg/m^2 and any cardiac RT dose was associated with a risk of abnormal GLS (7). It is currently unknown whether an abnormal GLS is associated with a LVEF <50% or clinical heart failure in CCS.

Diastolic dysfunction after cardiotoxic cancer treatment has also been described in CCS (8,96). In the St. Jude Lifetime cohort, diastolic dysfunction grade 1 to 3 (based on peak mitral flow velocity, mitral septal and lateral early diastolic velocity and left atrial volume) was detected in 11% of all CCS exposed to cardiotoxic treatment and in 8.7% with normal LVEF (7). One must be aware of the difficulties in the classification of diastolic dysfunction and there is a question of whether grading diastolic dysfunction according to the 2016 recommendations (97) has added value in CCS. Whether diastolic dysfunction is associated with asymptomatic systolic dysfunction and predictive of heart failure development warrants further investigation.

Cardiac MRI

Cardiac MRI is a well-suited imaging technique because geometric assumptions are not needed and the high resolution images enables accurate function assessment with high reproducibility (98). A study in 114 adult survivors demonstrated a significant difference in mean LVEF measured by MRI (55.9%) and 2-dimensional echocardiography (61.0%). Cardiomyopathy (LVEF<50% measured with MRI) was identified in 12 CCS (11%) previously undiagnosed by 2-dimensional echocardiography (91). The added value of this modality could lie in the abilities of tissue characterization (i.e. edema and fibrosis), right ventricle systolic function assessment, precise volumetric and strain assessment of other cardiac chambers aside from the LV. Thus, cardiac MRI enables evaluation of structural and functional changes induced by cancer treatment. Yet, studies investigating the role of cardiac MRI in CCS are scarce (99-102).

Blood biomarkers and electrocardiography

The limited diagnostic value of the blood biomarkers N-terminal pro-B-type natriuretic peptide and (high-sensitive) cardiac troponins in the detection of myocardial dysfunction by echocardiography more than one year after cancer diagnosis was shown in a

recent systematic review (103). Conflicting results on the predictive value of natriuretic peptides and troponins measured during cancer treatment for subsequent anthracycline cardiomyopathy exist in CCS (104,105). In adult cancer patients, the predictive value of elevated high-sensitive cardiac troponins during cancer treatment for early-onset cardiotoxicity may be more suggestive at specific timepoints (93,106).

ECG parameters may also aid in the prediction of myocardial dysfunction. A recent study in anthracycline treated CCS demonstrated that the QTc interval after chemotherapy was associated with subsequent LV dysfunction (107).

Guidelines for surveillance and treatment of cardiac disease in childhood cancer survivors

The IGHG aims to develop guidelines for surveillance of survivors of childhood cancer and young adult survivors by a global, interdisciplinary collaboration (108). Within the guideline development process, recommendations are formulated based on existent national follow-up guidelines and evidence summaries (109-112). Recommendations cover the clinical questions 1) who needs surveillance?, 2) which surveillance modality should be used?, 3) at what frequency and for how long should surveillance occur?, and 4) what should be done when abnormalities are found?

Cardiomyopathy surveillance guideline

The IGHG cardiomyopathy surveillance guideline was published in 2015 (113) and efforts are underway to update this guideline. It serves to define risk groups for the development of cardiomyopathy, based on cardiotoxic exposure. CCS treated with anthracycline doses ≥250 mg/m^2, chest RT dose ≥35 Gy or a combination of anthracyclines ≥100 mg/m^2 and chest RT dose ≥15 Gy are regarded as high risk. Anthracycline doses of 100-250 mg/m^2 or chest RT doses 15-35 Gy are regarded as moderate risk, and anthracycline doses <100 mg/m^2 as low risk. Echocardiographic surveillance is strongly recommended every 5 years or more frequently in high-risk CCS. It is reasonable to also surveil every 5 years in moderate- and low-risk CCS. Surveillance should start no later than two years after the completion of cardiotoxic therapy. The IGHG furthermore strongly recommends routine screening for and management of cardiovascular risk factors and counseling on smoking cessation and regular exercise.

Participation rates of high-risk CCS to guideline-based echocardiographic surveillance were shown to be less than one-third. In one RCT, telephone counselling more than

doubled the participation rate in the subsequent year, after correction for recommended surveillance frequency (114).

Until now, the IGHG did not formulate treatment recommendations for cardiomyopathy in CCS. When abnormalities are detected, this guideline recommends referral to a cardiologist. Clinical practice guidelines applied by (pediatric) cardiologists after referral are summarized in section 4.2.4.

Coronary artery disease surveillance guideline

The IGHG is currently finalizing a guideline for asymptomatic CAD surveillance in childhood, adolescent and young adult cancer survivors (115). Preliminary studies suggest that there is insufficient evidence to recommend a particular surveillance modality in asymptomatic childhood cancer survivors treated with chest RT. Emphasis is placed on awareness of premature CAD risk in survivors treated with chest RT. Risk assessment and surveillance and management of modifiable cardiovascular risk factors is needed. Knowing that there is already a difference in the incidence of CAD between CCS and siblings in their late twenties, clinicians should be aware of the potential atypical presentation of CAD in younger patients (17,109).

Other cardiac disease surveillance guidelines

As the modality of choice for the evaluation of valvular disease is echocardiography, assessment of valve function and structure are usually incorporated in the surveillance of CCS at risk with chest RT doses >15 Gy (113). Furthermore, assessment of pericardial structural abnormalities is possible as well. When abnormalities are detected, a cardiologist should be consulted, as specified in some national guidelines (109,111). To detect arrhythmia in an early phase, some national groups suggest performing an electrocardiogram at the initiation of long term follow-up (109,111).

Guidelines for management of cardiomyopathy in CCS

The IGHG cardiomyopathy guidelines refer to (pediatric) cardiology guidelines for further investigation and management of cardiac abnormalities (116-118). However, an exact threshold for abnormal systolic function is not defined. In the general adult population, a LVEF <40% is a robust indicator that medical therapy reduces mortality, regardless of heart failure symptoms. Treatment decisions for patients with a LVEF 40-49% should be a ‘shared decision’ balancing prognosis, heart failure symptoms and the individual’s

treatment tolerance (117,118). In practice, these thresholds are often extrapolated to CCS in the absence of survivor specific evidence.

Table 1 Future Directions in Cardio-Oncology Research in Childhood Cancer Survivors

Future research directions	Study design(s) to answer research question
Cardiac diseases	
Detailed risk and risk factor analysis of cardiac diseases after childhood cancer	Cohort studies and case control studies
Prevention of anthracycline cardiotoxicity	
Safety and effectiveness of dexrazoxane	RCTs and observational studies in high risk survivors, and risk prediction model guided studies.
Effectiveness of liposomal anthracyclines	
Effectiveness of longer infusion duration	
Effectiveness of pharmacological heart failure treatments	A RCT on low dose carvedilol in high risk CCS is ongoing (124)
Management of cardiovascular risk factors	
Effectiveness of risk factor modifications to prevent cardiovascular events in CCS	Prospective trials and RCTs in CCS with cardiovascular risk factors present
Effectiveness of lifestyle interventions in CCS	Prospective trials and RCTs in CCS
Risk prediction models	
Improvement with additional predictors (genetic, echocardiography, ECG and blood biomarkers)	Cohort studies with validation in an independent cohort
Benefit of longitudinal measurements to update individual risk predictions	Landmark analysis or joint modeling within cohort studies with external validation
The incremental predictive value of machine learning algorithms compared to classical regression	Multicenter cohort studies with a large number of events.
Clinical impact of prediction models	Cluster RCTs, decision curve analysis
Early detection of cardiac disease	
Usefulness of (strain) imaging, ECG parameters and blood biomarkers in early detection	Cohort studies, (cluster) RCTs of different surveillance strategies
Identification of novel blood biomarkers for cardiac disease	Proteomics/metabolomics in case-control studies with validation in cohort studies.
Genetics	
Genetic susceptibility for other diseases than anthracycline cardiomyopathy	Cohort studies with uniform cardiotoxic event definitions, replication in independent cohorts
Identification of novel genetic variants	GWAS or WGS in large (multicenter) cohort studies
Clinical usefulness of genetic risk stratification	Cohort studies with time to event analysis

CCS = childhood cancer survivors; ECG = electrocardiography; GWAS = genome-wide association studies; RCT = randomized controlled trial; WGS = whole-genome sequencing.

There is a lack of evidence to support treatment recommendations in CCS. A Cochrane systematic review identified only one RCT that evaluated the initiation of ACE-inhibitors for CCS with asymptomatic cardiac dysfunction (119). This study only showed

improvement in left ventricular wall stress by echocardiography. Possible reasons for failure to demonstrate an effect on clinical endpoints are the relatively short follow-up time (median 2.8 years) and liberal inclusion criteria (120).

The European Society of Cardiology published a position paper for the diagnosis and management of cancer patients and survivors in adult cardiology (121). The paper recommends prompt initiation of an ACE-inhibitor and β-blocker in those with cardiac dysfunction during cancer therapy, based on the high risk of developing heart failure. However, these recommendations were not based on RCT data. In long-term follow-up, general heart failure guidelines should be followed (117,118).

FUTURE PERSPECTIVES

Looking forward, there is a critical need for prospective and interventional studies to address most open research questions (Table 1). The current lack of intervention studies in CCS may be due to the long follow-up required for clinical events. Therefore, initially, intermediate imaging or blood biomarker outcomes may be useful as a proof of concept before conducting larger trials.

The safety and effectiveness of primary prevention strategies, including dexrazoxane, and secondary prevention strategies, such as modification of cardiovascular risk factors and treatment of asymptomatic myocardial dysfunction, can ideally be studied in RCTs or large observational studies. Prevention and surveillance may be further individualized with prediction model guided care after evaluation of their clinical impact.

Myocardial fibrosis and edema quantification with cardiac MRI are promising techniques to improve risk stratification and may facilitate earlier detection (40). The usefulness of echocardiographic strain imaging, ECG and blood markers in the early detection of cardiotoxicity in long-term childhood cancer survivors is currently being investigated in the Dutch LATER cohort study (122). In addition, modeling complex interactions and non-linear relationships between predictors and outcomes with machine learning algorithms may be a valuable addition to classic regression models in childhood cancer survivors when samples sizes are sufficient (123).

CONCLUSIONS

Cardiac disease after the treatment of childhood cancer is an important health problem for survivors of childhood cancer. Optimal survivorship care, including collaboration between pediatric oncologists and cardiologists, is needed to detect and treat cardiac abnormalities in an early phase. Over the past decade, a large body of evidence on cardiac diseases in CCS has been collected through cohort studies, that can improve current international surveillance guidelines. New insights into the impact of risk factors such as mitoxantrone should be incorporated in discussions on new treatment protocols for children with cancer and in guidelines for follow-up care. Apart from the treatment-related risk, lifestyle interventions may be important to modify cardiovascular risk factors and prevent cardiovascular events in aging survivors. Prediction models that have been developed for heart failure, ischemic heart disease and cardiovascular mortality await clinical impact analysis to guide individualized preventive measures, surveillance and treatment decisions. A better understanding of genetic susceptibility for anthracycline-induced cardiomyopathy and underlying pathophysiological mechanisms has the potential to improve both risk stratification and the development of primary and secondary prevention strategies. Translating research into the care for survivors is complex and requires a multi-disciplinary approach from researchers, epidemiologists, (pediatric) oncologists and cardiologists.

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SUPPLEMENTAL MATERIAL

Supplemental table 1. (Pubmed search 06-04-2020) and Supplemental table 3. (Overview of replicated genetic variants that alter the risk for anthracycline-induced cardiomyopathy in childhood cancer cohorts) are not included in this thesis. It can be found online in: JACC CardioOncol. 2020 Sep 15;2(3):363-378. doi: 10.1016/j.jaccao.2020.08.006. eCollection 2020 Sep.

Supplemental table 2. Validated risk prediction models for cardiotoxic events in long-term childhood cancer survivors.

	Chow et al 2015[1]	**Chow et al 2018[2]**	**Chen et al 2020[3]**	**Oikonomou 2018[4]**
Outcome	Heart failure at age 40	Ischemic heart disease at age 50	Heart failure and ischemic heart disease at age 50	Cardiovascular mortality
Sample size	Derivation: 13,060 Validation: 3,421	Derivation: 13,060 Validation: 3,204	Derivation: 7,076 Validation: 7,075	Derivation: 22,374 Validation: 6,437
Prediction timepoint	5 years after diagnosis	5 years after diagnosis	Age 20-35 years	5 years after diagnosis
Predictor selection	Stepwise backwards selection, based on p-value	Stepwise backwards selection on p-value	A priori	P<0.05 in multivariable Cox regression with 1000 bootstrap analysis
Predictors	Female sex, age at cancer diagnosis, anthracycline dose, chest-RT dose	Male sex, chest-RT dose	Heart failure: Male sex, age at diagnosis, anthracycline dose, chest-RT dose, diabetes, dyslipidemia, hypertension Ischemic heart disease: Female sex, chest-RT dose, diabetes, dyslipidemia, hypertension	Age at diagnosis, male sex, lymphoma history, any radiation, race
Discrimination	C-statistic 0.68-0.82	C-statistic 0.66-70	C-statistic 0.69-0.70 (both events)	C-statistic: 0.75 derivation, 0.72 validation
Calibration	Not performed	Not performed	Good calibration	Not performed
Validation	External in another cohort	External in another cohort	Internal (split sample analysis)	Internal (split sample analysis)
Clinical impact analysis	Not performed	Not performed	Not performed	Not performed

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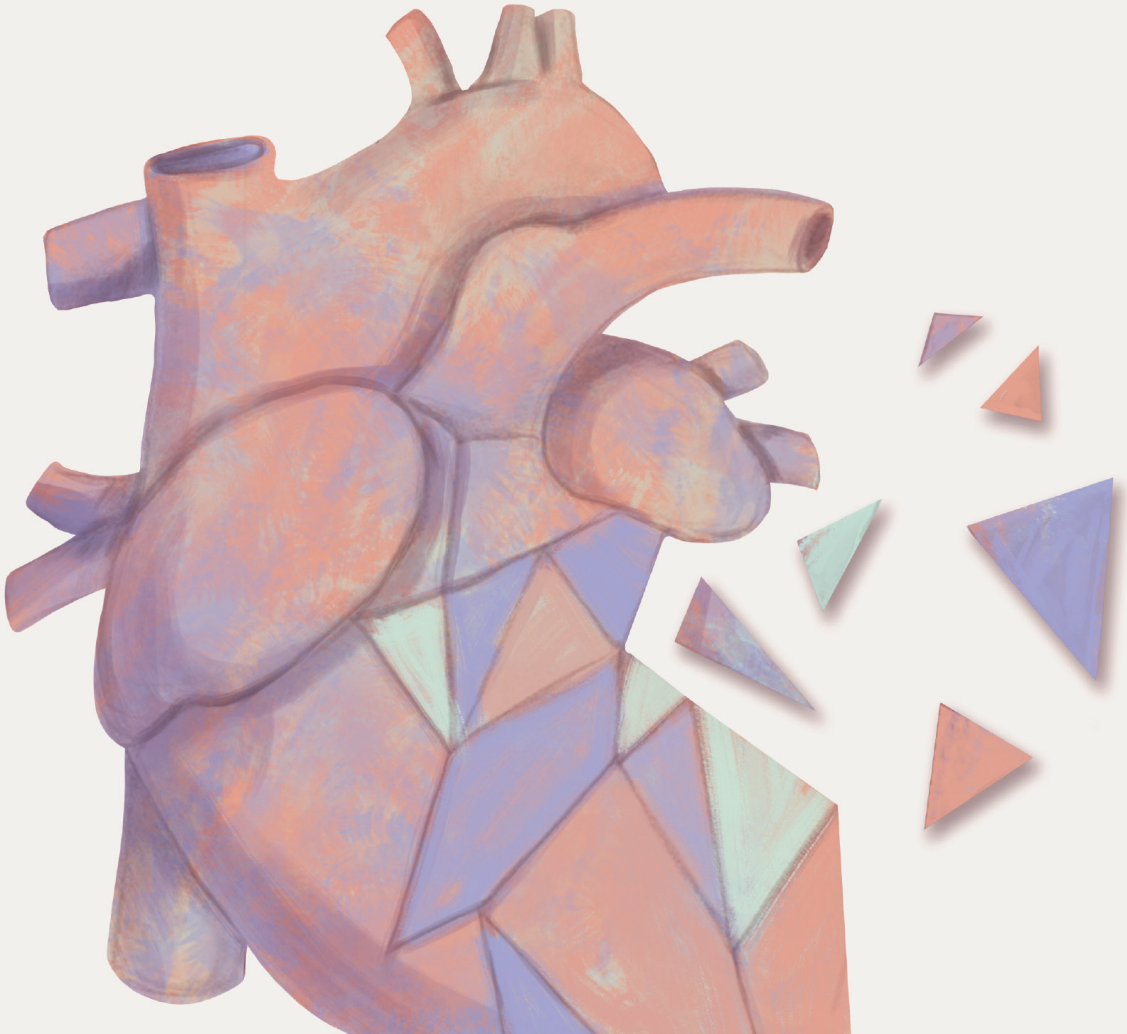

CHAPTER 3

Risk stratification

3.1

RISK FACTORS FOR HEART FAILURE AMONG PAN-EUROPEAN CHILDHOOD CANCER SURVIVORS: A PANCARESURFUP & PROCARDIO COHORT AND NESTED CASE-CONTROL STUDY

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Journal of Clinical Oncology. 2023 Jan 1;41(1):96-106

ABSTRACT

Purpose – Heart failure (HF) is a potentially life-threatening complication of treatment for childhood cancer. We evaluated the risk and risk factors for HF in a large European study of long-term survivors. Little is known of the effects of low doses of treatment, which is needed to improve current treatment protocols and surveillance guidelines.

Methods –This study includes the PanCareSurFup and ProCardio cohort of ≥5-year childhood cancer survivors diagnosed between 1940 and 2009 in seven European countries (n=42,361). We calculated the cumulative incidence of HF and conducted a nested case-control study to evaluate detailed treatment-related risk factors.

Results – The cumulative incidence of HF was 2% (95% CI 1.7-2.2) by 50 years of age. The case-control study (n=1000) showed that survivors who received a mean heart RT dose of 5-<15 Gray have an increased risk of HF (OR 5.5, 95% CI 2.5-12.3), when compared to no heart RT. The risk associated with doses 5-<15 Gy increased with exposure of a larger heart volume. In addition, the HF risk increased in a linear fashion with higher mean heart RT doses. Regarding cumulative anthracycline dose, survivors who received ≥100 mg/m^2 had a substantially increased risk of HF and survivors treated with a lower dose showed no significantly increased risk of HF. The dose-response relationship appeared quadratic with higher anthracycline doses.

Conclusion –Survivors who received a mean heart RT dose of ≥5Gy have an increased risk of HF. The risk associated with RT increases with larger volumes exposed. Survivors treated with <100 mg/m^2 cumulative anthracycline dose have no significant increased risk of HF. These new findings may have consequences for new treatment protocols for children with cancer and for cardiomyopathy surveillance guidelines.

BACKGROUND

Developments in the treatment for children with cancer have improved survival considerably over recent decades[1]. However, long-term survivors are at risk of adverse effects induced by cancer and its treatment. One of the most severe effects is cardiotoxicity. This may occur as asymptomatic myocardial dysfunction and can progress to symptomatic heart failure (HF), which is related to increased morbidity and mortality[2-7].

Previous studies among childhood cancer survivors (hereafter 'survivors') identified treatment-related risk factors for HF, including anthracyclines, mitoxantrone, and radiation therapy (RT) where the heart was in the radiation field[4,8-12]. Anthracycline analogues that have been linked to cardiotoxicity comprise doxorubicin, daunorubicin, epirubicin, and idarubicin. Mitoxantrone is an anthraquinone and structurally comparable to doxorubicin[13]. Of these chemotherapeutic agents, mitoxantrone has the greatest cardiotoxic potential which may be related to differences in underlying pathophysiology[14,15]. Other potential risk factors for HF are cyclophosphamide, sex, age at cancer diagnosis, and presence of traditional cardiovascular risk factors[2,4,7,16-18].

Surveillance of myocardial function after cardiotoxic treatment is of great importance to detect treatable abnormalities at an early stage[19]. The International Guideline Harmonization Group (IGHG) formulated cardiomyopathy surveillance recommendations in 2015 for survivors treated with anthracyclines (all doses) and survivors treated with radiotherapy involving the heart region of ≥15 Gray (Gy). Furthermore, this group highlighted future directions for research including the risk of symptomatic HF in survivors treated with <15 Gy chest RT as little was known about the effects[19]. New evidence for low doses of cardiotoxic treatments is needed to guide both updates of cardiomyopathy surveillance strategies and designs of treatment regimes.

Pooling data from two EU-funded consortia, the PanCareSurFup (PCSF) cardiac study[20] and ProCardio[21], created a large cohort of survivors (n=42,361) to investigate low treatment doses of anthracyclines and cardiac radiation therapy and the nature of dose-responses, by using phantom based radiation dosimetry including dose-volume histogram indicators. This latter technique calculates the estimated dose received by the organ at risk.

METHODS

In 2011 collaborative efforts initiated the PCSF cardiac study[22] and ProCardio and designed them to be complementary with a view to pooling data. We conducted a cohort study and a nested case-control study using these data. We described the exact process below and visualized it by a flowchart in Supplement A.

Study population

We included ≥5-year survivors in whom cancer was diagnosed <20 years of age between 1940 and 2009. The PCSF cardiac study comprised eight European sub-cohorts from France, Hungary, Italy (two sub-cohorts), the Netherlands, Slovenia, Switzerland, and the United Kingdom (UK). The ProCardio project comprised survivors from France and the UK. The inclusion criteria, which are listed in Supplement B, differed slightly between the sub-cohorts. The study was performed after approval by a local Human Investigations Committee. In each country regulations are different, relating to informed consent.

Identification of survivors with heart failure

We identified survivors with HF (hereafter 'case') as a first event by using multiple strategies, for example linkage to population-based databases and patient-based questionnaires. A case was defined as having symptomatic HF graded according to the Common Terminology and Criteria for Adverse Events[23] as grade 3, 4, and 5 (see Supplement C). The exact methods are described by Feijen et al.[22].

Case-control study: control selection

We randomly selected controls by density sampling and matched them to cases with HF (ratio 1:1) on sub-cohort, sex, age at first cancer diagnosis (± 1 year), and calendar year of first cancer diagnosis (± 3 year). The length of follow-up after first cancer diagnosis of controls was at least as long as the interval between cancer diagnosis and HF in the matched case, but controls had to be HF free. When no suitable control could be found, the calendar period criterion was relaxed (maximum 10 years). If still no eligible control was available then age at cancer diagnosis was relaxed (maximum 3 years).

Data collection

For the cohort study, we collected baseline characteristics for all survivors included in the analysis. This data included sex, month and year of birth, month and year of first cancer

diagnosis, morphology code, type of treatment, and the month and year of the start of treatment[22]. For the case-control study, we collected details of treatment for all cases and controls from medical records by using a standardized extraction form. We collected data for each cycle of each cytotoxic agent to enable calculation of cumulative dose (or equivalent[14,24,25]). We performed radiation dosimetry for the whole body including seven parts of the heart for all cases and controls who received RT, as previously described[26-28]. With dosimetry we calculated the estimated average of the maximum dose that was given to different parts of the whole heart, this measure is reflected by mean heart RT dose. In addition, we created dose volume variables by calculating the percentage of heart volume that received at least 5 (V5), 10 (V10), 15 (V15), 20 (V20) or 30 (V30) Gy. The variable V5-15 reflects the percentage of the cardiac volume that received a maximum dose of 5 to 15 Gy and the variable V15 reflects the percentage of the cardiac volume that received at least 15 Gy. We collected all treatment data until date of the cardiac event for cases and for the same period of follow-up from childhood cancer diagnosis for the matched controls.

Statistical analysis

For the cohort study the main outcome of interest was the first occurrence of symptomatic HF. Time at risk started 5 years after the first primary cancer diagnosis. Cardiac follow-up ended at the first occurrence of HF, death for deceased individuals or at last date of exit from cardiac follow-up. To limit follow-up bias, we fixed the final end-of follow-up date separately for each sub-cohort as the last date on which cardiac follow-up was available for ≥80% of sub-cohort-members, see Supplement E. We calculated the cumulative incidence of symptomatic HF with attained age as the time scale and taking death into account as a competing risk[29]. We analyzed cumulative incidence for the overall cohort, by sub-cohort, and by treatment period until the number at risk was <100. We performed a Gray's test to test for unadjusted significant differences between the cumulative incidences[30].

In the case-control study, we included all cases identified in the cohort study (100% of all sub-cohorts-members) and used a conditional logistic regression model to estimate odds ratios (ORs). The model included treatment-related exposures based on the literature and clinical knowledge[7,31-33]. See Supplement D for the complete list of chemotherapy agents that were tested. We started with a "baseline" model including cumulative anthracycline dose and mean heart RT dose since these are well-established risk factors for HF[2,7,12]. Thereafter, we expanded the baseline model by adding each potential covariate to the

model and compared it to the baseline model with a likelihood ratio test. For the final model we evaluated evidence of interaction between treatment variables and age at diagnosis. In addition, we analyzed heart RT dose-volume variables by including them instead of mean dose. We used R-studio (version 6.1.1) to analyze non-continuous treatment exposures and we used Epicure software[34] to evaluate continuous exposures by fitting a linear model for the excess odds ratio (EOR) and to evaluate departures from linearity. For all analyses, we defined statistical significance as a 2-sided p-value of less than 0.05.

RESULTS

The characteristics of survivors included in the cohort study are presented in Supplement F. The cohort included a total of 36,205 survivors (45% were female). The UK sub-cohort contributed 46%. The median age of the survivors was 5.8 years at the time of diagnosis and was 29.7 years at the end of follow-up. The most frequent cancer diagnoses were leukemia (27%), lymphoma (15%), central nervous system tumors (18%), and sarcoma (12%).

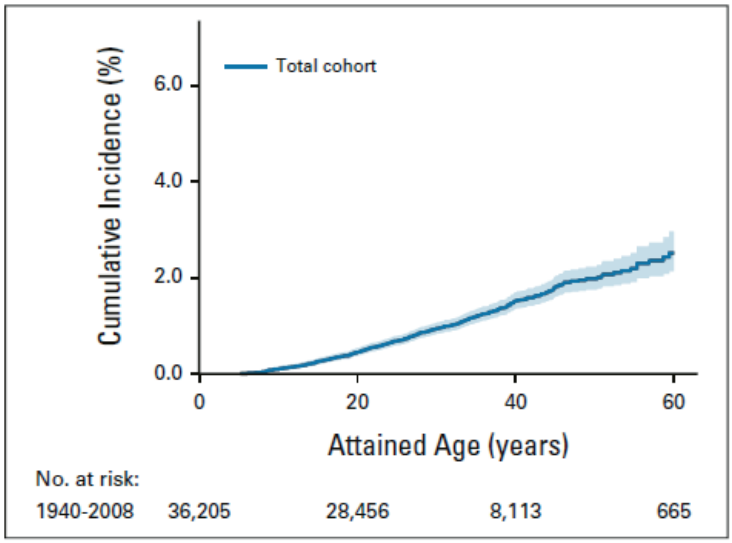

Figure 1. Cumulative incidence of heart failure for all survivors (including all types of treatment) with attained age as the time scale. Shaded: 95% CI.

Figure 1 shows the cumulative incidence of HF by attained age. By 50 years of attained age, the cumulative incidence of HF was 2.0% (95% CI 1.7-2.2). Supplement G illustrates

the variation in cumulative incidence of HF between the sub-cohorts. The latest time point we could analyze all different sub-cohorts was 30 years of age at which the cumulative incidence ranged between 0.2 and 2.6%. For France, the UK, and the Netherlands the risk by 50 years of age was available and the cumulative incidence ranged from 1.0 to 5.2%. See Supplementary file H for the characteristic of the survivors by sub-cohort. The cumulative incidence of HF was greater among those with cancer diagnosed from 1980 onwards than among those diagnosed before, see Figure 2A. Figure 2B shows that the cumulative incidence of cardiac mortality due to HF was lower in the treatment period 1990-2008 compared to 1980-1990.

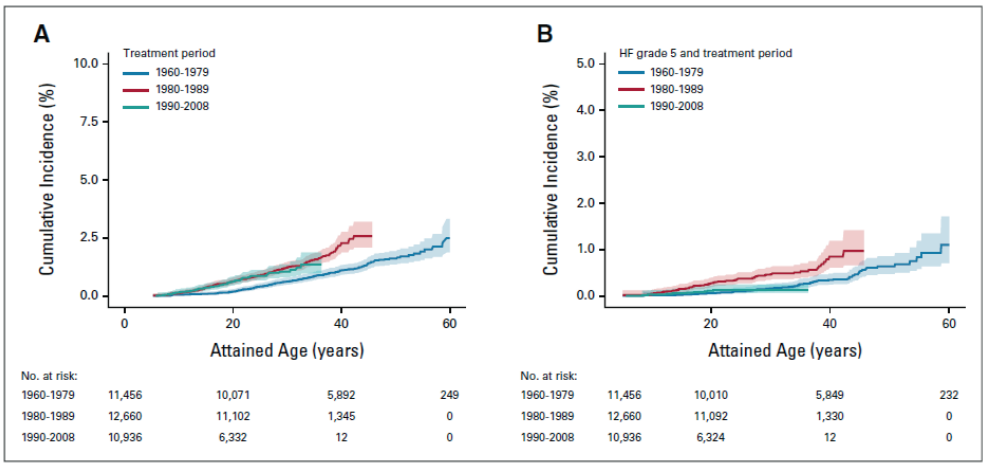

Figure 2. (A) Cumulative incidence of HF for three different treatment periods: 1960-1979 (No. = 11,456 cohort members and No. = 150 cases), 1980-1989 (No. =12,660 cohort members and No. = 169 cases), and 1990-2008 (No. = 10,936 cohort members and No. = 66 cases). Pairwise comparisons showed these degrees of significance: 1960-1979 versus 1980-1989, P=.0004; 1960-1979 versus 1990-2008, P=.00008; 1980-1989 versus 1990-2008, P=.3917. (B) Cumulative incidence of cardiacmortality because of HF for three different treatment periods: 1960-1979 (No.=11,456 cohort members and No. = 56 cases), 1980-1989 (No. = 12,660 cohort members and No. = 62 cases), and 1990-2008 (No. = 10,936 cohort members and No. = 9 cases). Pairwise comparisons showed these degrees of significance: 1960-1979 versus 1980-1989, P=.0001; 1960-1979 versus 1990-2008, P=.73; and 1980-1989 versus 1990-2008, P=.0005. HF, heart failure.

The case-control study included 500 cases and 500 controls and their characteristics are demonstrated in Table 1. Of all survivors, 366 had not received any RT and the RT exposure was unknown for 1 case and 2 controls. Among the 631 survivors who received RT, dosimetry was impossible for 7 (1.1%) cases and 5 (0.8%) controls. The median of the mean heart RT dose in cases was 18.1 Gy, compared to 16.5 Gy in controls. The median cumulative anthracycline dose (including mitoxantrone) was 362 mg/m^2 in cases and 218 mg/m^2 in controls. Analyzing

mitoxantrone as separate exposure would have led to underpowered results because only 29 survivors (9 of them with missing dose) received this agent. Dexrazoxane treatment was equal between cases (n=4) and controls (n=4).

The final model included cumulative anthracycline dose and mean heart RT dose (Table 2). See Supplement I Table 1 for the likelihood ratio tests for all analyzed covariates. The ORs of HF significantly increased with both the cumulative anthracycline dose (p_{trend}=<0.0001) and mean heart RT dose (p_{trend}=<0.0001). When compared to survivors who did not receive anthracyclines, the OR associated with cumulative anthracycline doses <100 mg/m^2 did not reach statistical significance (2.3, 95%CI: 0.7-7.1), the OR for 100-<250 mg/m^2 was 5.8 (95%CI: 2.9-11.3) and the OR for ≥250 mg/m^2 was 21.2 (95%CI: 11.4-39.2). When compared to survivors with a mean heart RT dose of 0 Gy, a mean heart dose of <5 Gy was not associated with HF risk (1.3, 95% CI: 0.8-2.0), the OR for 5-<15 Gy was 5.5 (95% CI: 2.5-12.3), the OR for 15-<35 Gy was 9.0 (95% CI: 4.6-17.6) and the OR for ≥35 Gy was 22.6 (95%CI: 4.9-102.8). We also evaluated the non-continuous dose-response relationship in more detail, see Supplement I Table 2. Further analyses provided no evidence of an effect modification by age at diagnosis regarding the roles of anthracyclines or heart RT on the risk of HF, see Supplement I Table 3. We refer the reader to Supplement I Table 4 for the characteristics of the cases and controls who have only been exposed to heart RT and not to anthracyclines, and to Supplement I Table 5 for the characteristics of the cases and controls who have been exposed to a mean heart RT dose of 5-<15 Gy. In addition, we evaluated dose-volume RT variables instead of mean heart RT dose adjusted for cumulative anthracycline dose. In survivors who received a maximum heart RT dose of 5-<15 Gy, the OR of HF was significantly increased if ≥50% of the volume was exposed (OR 5.6; 95% CI 1.5-20.6). In survivors who received ≥15 Gy, the risk was already significantly increased if <50% of the heart was exposed (Table 3). Supplement I Table 6 demonstrates the results of the remaining dose-volume variables.

When fitting the continuous cumulative anthracycline dose as a linear term (adjusted for heart RT), there was a significant departure from linearity (Supplement I Table 7). The EOR per 100 mg/m^2 cumulative anthracycline dose was expressed by the following equation; EOR=-0.3(dose/100) + 1.6(dose/100)^2 (Figure 3A). For mean heart RT dose, the dose-response relationship (adjusted for anthracyclines) was linear and yielded an EOR of 5.1 per 10 Gy (Figure 3B).

Table 1. Characteristics of the Survivors Included in the Case-Control Study

Characteristics	Cases = 500 (100%)	Controls = 500 (100%)
Sex,[a] No. (%)		
Female	219 (43.8)	219 (43.8)
Sub-cohort,[a] No. (%)		
United Kingdom	129 (25.8)	129 (25.8)
France	195 (39)	195 (39)
Netherlands	105 (21)	105 (21)
Italy	18 (3.6)	18 (3.6)
Switzerland	11 (2.2)	11 (2.2)
Hungary	37 (7.4)	37 (7.4)
Slovenia	5 (1)	5 (1)
Type of childhood cancer, No. (%)		
Leukemias, myeloproliferative diseases and myelodysplastic diseases	85 (17)	73 (14.6)
Lymphomas and reticulo endothelial neoplasms	136 (27.2)	107 (21.4)
CNS and miscellaneous intracranial and intraspinal neoplasms	15 (3.0)	78 (15.6)
Neuroblastoma and other peripheral nervous cell tumors	42 (8.4)	37 (7.4)
Retinoblastoma	2 (0.4)	21 (4.2)
Renal tumors	64 (12.8)	81 (16.2)
Hepatic tumors	8 (1.6)	3 (0.6)
Bone tumors	57 (11.4)	23 (4.6)
Soft tissue and other extraosseous sarcomas	68 (13.6)	46 (9.2)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	13 (2.6)	18 (3.6)
Other malignant epithelial neoplasms and malignant melanomas	8 (1.6)	13 (2.6)
Other and unspecified malignant neoplasms	2 (0.4)	0 (0)
Age at childhood cancer diagnosis, years[a]		
Median (IQR)	5.8 (2.7-10.9)	5.6 (2.6-10.4)
0 - <5, No. (%)	222 (44.4)	228 (45.6)
5 - <10, No. (%)	135 (27)	118 (23.6)
10 - <15, No. (%)	119 (23.8)	126 (25.2)
≥15, No. (%)	24 (4.8)	28 (5.6)
Calendar year of diagnosis,[a] No. (%)		
<1980	202 (40.4)	208 (41.6)
1980 - <1990	212 (42.4)	212 (42.4)
1990-2008	86 (17.2)	80 (16)
Attained age, years		
Median (min-max)	27.0 (5.3 – 73.2)	26.4 (5.3-73.0)
<15, No. (%)	68 (13.6)	74 (14.8))
15 - <25, No. (%)	155 (31.0)	155 (31.0)
25 - <35, No. (%)	142 (28.4)	142 (28.4)
35 - <45, No. (%)	93 (18.6)	89 (17.8)
45 - <55, No. (%)	29 (5.8)	27 (5.4)
≥55, No. (%)	13 (2.6)	13 (2.6)

Characteristics	Cases = 500 (100%)	Controls = 500 (100%)
Follow-up duration, years[a]		
Median (min-max)	20.3 (5.0-62.5)	20.0 (5.0-62.0)
>5 - <10, No. (%)	79 (15.8)	85 (17.0)
10 - <20, No. (%)	167 (33.4)	161 (32.2)
20 - <30, No. (%)	155 (31.0)	159 (31.8)
30 - <40, No. (%)	75 (15.0)	72 (14.4)
≥40, No. (%)	24 (4.8)	23 (4.6)
Cardiotoxic treatment,[b] No. (%)		
No cardiotoxic treatment	23 (4.6)	125 (25)
Anthracyclines only	140 (28)	89 (17.8)
Heart RT only	108 (21.6)	189 (37.8)
Anthracyclines and heart RT	241 (44.1)	88 (17.6)
Unknown	15 (3.0)	9 (1.8)
Cumulative anthracycline dose,[c] mg/m²		
Median (IQR)	362 (248 - 476)	218 (125 - 331)
No, No. (%)	135 (27.0)	321 (64.2)
>0 - <100, No. (%)	9 (1.8)	22 (4.4)
100 - <200, No. (%)	36 (7.2)	49 (9.8)
200 - <300, No. (%)	55 (11)	38 (7.6)
300 - <400, No. (%)	73 (14.6)	37 (7.4)
≥ 400, No. (%)	125 (25)	19 (3.8)
Unknown, No. (%)	67 (13.4)	14 (2.8)
Mitoxantrone, No. (%)		
No	465 (93)	495 (99)
Yes	26 (5.2)	3 (0.6)
Unknown	9 (1.8)	2 (0.4)
Mean heart RT dose, Gy		
Median (IQR)	18.1 (9.4 – 28.3)	16.5 (5.5 – 23.3)
No, No. (%)	166 (33.2)	215 (43)
>0 - <5, No. (%)	138 (27.6)	195 (39)
5 - <15, No. (%)	55 (11)	25 (5)
15 - <35, No. (%)	111 (22.2)	53 10.6)
≥35, No. (%)	22 (4.4)	5 (5)
Unknown, No. (%)	8 (1.6)	7 (1.4)
Grade of validated heart failure, No. (%)		
Grade 3	231 (46.2)	NA
Grade 4	112 (22.4)	NA
Grade 5	157 (31.4)	NA
Vital status, No. (%)		
Alive	301 (60.2)	450 (90.0)
Deceased	199 (39.8)	50 (10.0)

Abbreviations: IQR, interquartile range; max, maximum; min, minimum; NA, not applicable; RT, radiotherapy.

[a]Matching variable to select controls (ratio 1:1): on subcohort, sex, age at first cancer diagnosis (±1 year), calendar year of first cancer diagnosis (±3 year), and length of follow-up.

[b]Cardiotoxic treatment = anthracyclines including mitoxantrone and/or mean heart RT dose > 0 Gy.

[c]Total cumulative anthracycline dose (mg/m²) + doxorubicin + (daunorubicin X 0.5) + (epirubicin X 0.8) + (idarubicin X 3) + (mitoxantrone X 10.5).

Table 2. Multivariable conditional logistic regression model of grade 3-5 heart failure by cancer treatment variables

Variable	Dose	Cases,[a] No.	Controls, No.	OR (95%CI)	p-value[b]
Total cumulative anthracycline dose, mg/m²	0	135	321	Ref	-
	>0 - <100	9	22	2.3 (0.7-7.1)	.2
	100 - <250	66	68	5.8 (2.9-11.3)	<0.0001
	≥250	223	75	21.2 (11.4-39.2)	<0.0001
	Missing[c]	67	14		p_{trend} = <0.0001
Mean heart RT dose, Gy	0	166	215	Ref	-
	>0 - <5	138	195	1.3 (0.8-2.0)	.4
	5 - <15	55	25	5.5 (2.5-12.3)	<0.0001
	15 - <35	111	53	9.0 (4.6-17.6)	<0.0001
	≥35	22	5	22.6 (4.9-102.8)	<0.0001
	Missing[d]	8	7		p_{trend} = <0.0001

Abbreviations: OR, odds ratio; Ref, reference group; RT, radiotherapy.

[a]Matching variables: subcohort, sex, age at first cancer diagnosis (±1 year), calendar year of first cancer diagnosis (±3 year), and length of follow-up after first cancer diagnosis.

[b]Calculated with the clogit function in R-studio.

[c]n = 9 cases and n = 2 controls unknown whether received anthracyclines versus n = 58 cases and n = 12 controls received anthracyclines but dose unknown.

[d]n = 1 cases and n = 2 controls unknown whether received radiotherapy versus n = 7 cases and n = 5 controls exposed but dose on heart unknown.

DISCUSSION

Insight in the risk factors for HF in survivors of childhood cancer is relevant for both the treatment of new children with cancer and for cardiac surveillance in survivors after cardiotoxic treatment. This large pan-European nested case-control study shows important new findings. We show that survivors who received a comparatively low mean heart RT dose of 5-<15 Gy had a 5-times higher risk of HF compared to survivors who did not receive RT in the heart region, especially when more than half of the heart was exposed to low RT doses. Furthermore, we did not identify a significant increased risk of HF for survivors treated with <100 mg/m² cumulative anthracycline dose.

As emphasized by the IGHG cardiomyopathy surveillance guideline[19], little was known about the risk of HF for survivors exposed to lower doses of RT. Consequently, no recommendations could be made for survivors treated with chest RT <15 Gy and a moderate recommendation (based on weak quality evidence) could be made for 15-35 Gy[19]. Previous studies in childhood cancer survivors have not found evidence that heart RT doses <15 Gy calculated with dosimetry were associated with HF[2,12,16,35,36]. This could

be the result of insufficient statistical power. Recently, Bates et al. demonstrated that phantom-based mean heart RT doses of 10-20 Gy are associated with a higher risk for HF in 24,214 survivors from the Childhood Cancer Survivor Study (CCSS) (n=371 HF events), however they could not demonstrate a dose-volume relationship in this dose range[11]. Within our large case-control study derived from an underlying cohort exceeding 50,000 survivors, we found that survivors treated with a mean heart RT dose 5-<15 Gy are at risk of HF. Our results could be of great clinical importance, because, based on our data, a part of the survivors who are at risk will be labelled as low risk by current cardiomyopathy surveillance strategies [19] (see Supplement I Table 8 & 9). We recognize that this concerns a small absolute number of cases, however, the proportion of survivors exposed to low mean heart RT doses is likely growing as a result of developments in radiotherapy techniques[37].

Mean heart RT dose will be more and more available as it is part of current treatment planning in many institutions. Therefore, we propose to include this measure in the current cardiomyopathy surveillance guideline and recommend echocardiographic follow-up for survivors treated with a mean heart RT dose of ≥5 Gy. However, mean heart RT dose is not available for survivors who received radiotherapy prior to the introduction of advanced RT planning systems[38]. For these survivors, the prescribed chest RT dose can be used as a surrogate for the maximum heart RT dose (calculated by dosimetry) in our dose-volume analysis. This analysis showed that in survivors treated with a maximum RT dose of 5-<15 Gy the risk increased when larger cardiac volumes were exposed (≥50% of the total volume). Accordingly, one could consider monitoring survivors who were exposed to a prescribed chest RT dose of 5-<15 Gy when an experienced member of the paediatric radiotherapy planning team estimates that at least 50% of the heart was included in the original treatment field.

Regarding mean heart RT dose and the risk of HF, we show a linear dose-response relationship when adjusted for anthracyclines. In contrast, a case-control study of van Nimwegen et al., who included 369 adolescent or adult 5-year survivors of Hodgkin Lymphoma, demonstrated a nonlinear dose-response relationship[39]. However, this was not adjusted for anthracycline dose, and the HF-cases were older, and exposed to higher doses of mean heart RT which may have influenced their results.

Table 3. Multivariable Conditional Logistic Regression Models[a] of Grade 3-5 Heart Failure by Volume of the Heart Exposed to the Individual Patients' Maximum Heart RT Dose

Variable	Volume of the heart, %	Cases,[b] No.	Controls, No.	OR (95%CI)	p-value
5 to <15 Gy[c]	No RT	166	215	Ref	-
	0 - <10	117	179	1.3 (0.7-2.2)	0.4
	10 - <50	7	5	1.9 (0.4-8.9)	0.4
	≥ 50	27	5	5.6 (1.5-20.6)	0.01
	Missing[2]	8	7		
≥ 15 Gy	No RT	166	215	Ref	-
	0 - <10	176	213	1.9 (1.1-3.1)	0.01
	10 - <50	21	18	3.4 (1.1-9.0)	0.01
	50 - <90	68	39	9.4 (4.4-20.1)	<0.0001
	≥90	61	8	14.6 (6.0-35.5)	<0.0001
	Missing[2]	8	7		

Abbreviations: OR, odds ratio; Ref, reference group; RT, radiotherapy.

[a]all models were adjusted for cumulative anthracycline dose

[b]Matching variables: subcohort, sex, age at first cancer diagnosis (±1 year), calendar year of first cancer diagnosis (±3 year), and length of follow-up after first cancer diagnosis.

[c] all the patients are included in de model: the factor variable included also n=175 cases and n=89 controls who received ≥15 Gy to any volume of the heart (OR 8.3, 95% CI 4.5-15.5).

[d]n=1 cases, n=2 controls unknown whether received radiotherapy versus n=7 cases, n=5 controls exposed but dose on heart unknown.

Currently, the IGHG cardiomyopathy surveillance guideline includes a moderate (based on weak quality evidence) recommendation for cardiac surveillance for survivors treated with <100 mg/m^2 anthracyclines[19]. Our study did not identify a significant increased risk of HF for survivors treated with <100 mg/m^2 cumulative anthracycline dose, in line with previous studies[16,36,40]. Nevertheless, there were some cases with HF in this treatment group; possible reasons for this include the presence of cardiovascular risk factors and genetic susceptibility to anthracycline induced-cardiomyopathy[36,40]. We calculated the cumulative anthracycline dose based on the results of Feijen et al. and included the mitoxantrone dose[14,24]. The previous studies used different doxorubicin equivalent ratios, so a comparison with our study can be limited[16,36,40]. Previous literature suggested that the dose-response of HF and cardiac events more generally, might increase substantially with higher anthracycline doses[40,41] which is confirmed by our study. Based on our data, the dose-response relationship appeared quadratic and Figure 3 reflects that the risk of HF increases exponentially with higher cumulative anthracycline doses. The results of our study and the cost-effectiveness study of Ehrhardt et al.[42] strengthen the need to reconsider the current recommendation for cardiac screening of low risk survivors[19].

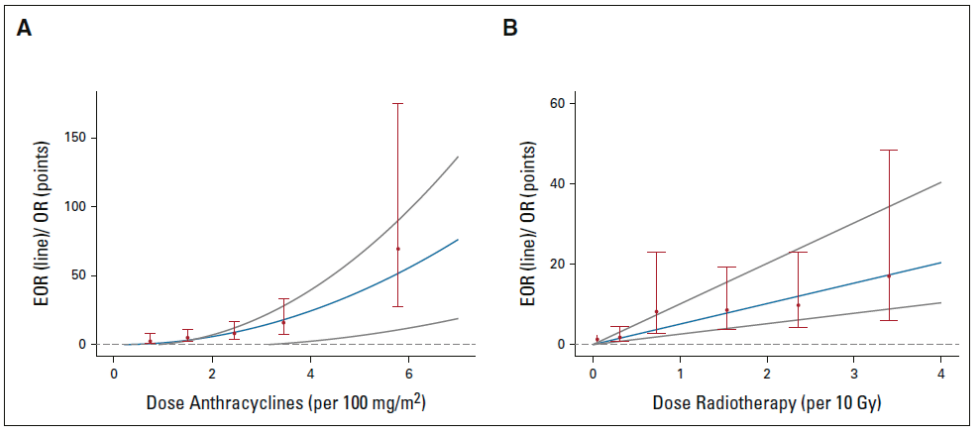

Figure 3. (A) The ORs and corresponding 95% CIs (red dots and bars) of developing heart failure by the received total cumulative anthracycline dose and the fitted linear EOR and corresponding 95% CIs per 100 mg/m^2 anthracyclines (solid blue and gray line), both of which were adjusted for mean heart RT dose. ORs were calculated relative to survivors treated without anthracyclines and are plotted at the mean cumulative anthracyclines dose of the controls within each relevant dose category. (B) The ORs and corresponding 95% CIs (red dots and bars) of developing heart failure by the received mean heart RT dose and the fitted linear EOR and corresponding 95% CIs per 10 Gy mean heart RT (solid blue and gray line), both of which were adjusted for cumulative anthracycline dose. ORs were calculated relative to survivors treated without heart RT and are plotted at the mean cumulative radiation dose of the controls within each relevant dose category. EOR, excess odds ratio; OR, odds ratio; RT, radiation therapy.

In the cohort study we evaluated the trend in cumulative incidence of both HF (grade ≥3) and HF related mortality (grade 5). An important finding is that the cumulative incidence of HF increases more steeply with attained age in survivors treated ≥1980. In contrast to our results, in the CCSS the cumulative incidence of HF was lower in the 1990s compared to earlier decades[2]. Although detailed treatment information is not available for our cohort, we postulate that the difference in the degree of changes in treatment intensity[2,7] and the difference in era grouping could play a role. In addition, the introduction of survivorship care in the 1990s potentially resulted in more survivors being monitored and being aware of cardiac diseases and thus more likely to visit the GP or late-effects clinic in Europe. This could have led to more HF diagnoses after 1990. Furthermore, we showed that the cumulative incidence of HF-related mortality is lower for survivors who are diagnosed ≥1990 when compared to 1980-1989. As in the general population[43], this may be related to improvement in early diagnosis and treatment. As demonstrated in Supplementary file G, the cumulative incidence of HF varies between the sub-cohorts. This is most likely caused by different proportions of survivors exposed to cardiotoxic

treatment as a results of the sub-cohort specific inclusion criteria. Also the differences in healthcare systems may have influenced the detection of grade 3 HF.

Beside the strengths of our study where we were able to provide precise estimates of HF risk in the low doses for heart RT and anthracycline, some limitations need to be considered. A potential limitation of the case-control study is that traditional cardiovascular risk factors could not be analyzed because data on for example hypertension, diabetes mellitus, and smoking status was missing for >50% of cases and controls. However, such risk factors are unlikely to be strong confounding factors in the relationship between the investigated treatment factors and risk of HF. Regarding Supplement I Table 8 and 9, the actually risk might be underestimated for some cases as a result of missing anthracycline dose. Furthermore, the cumulative incidence of HF may be underestimated due to the methods of HF ascertainment in the cohort study. Despite the advantages of linkage, it is possible that some cases were missed[44]. In the UK most of the period at risk was covered by a questionnaire completed by the survivor followed by medical record validation; only a minority of follow-up was covered by linkage alone.

In conclusion, this study provides new evidence that survivors who received a mean heart RT dose of 5-<15 Gy have an increased risk for HF, especially when more than half of the heart was exposed to RT. Furthermore, this study did not identify a significant increased risk of HF for survivors treated with <100 mg/m^2 cumulative anthracycline dose. These new findings may have consequences for new treatment protocols for children with cancer and for cardiomyopathy surveillance guidelines.

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SUPPLEMENTAL MATERIAL

A. Flowchart of the participants, data collection and statistical analysis

B. Inclusion criteria per sub-cohort

C. Definitions of heart failure

D. Overview of analysed chemotherapy groups

E. Completeness of cardiac follow-up in ≥5-year survivors from the PanCareSurFup cardiac study

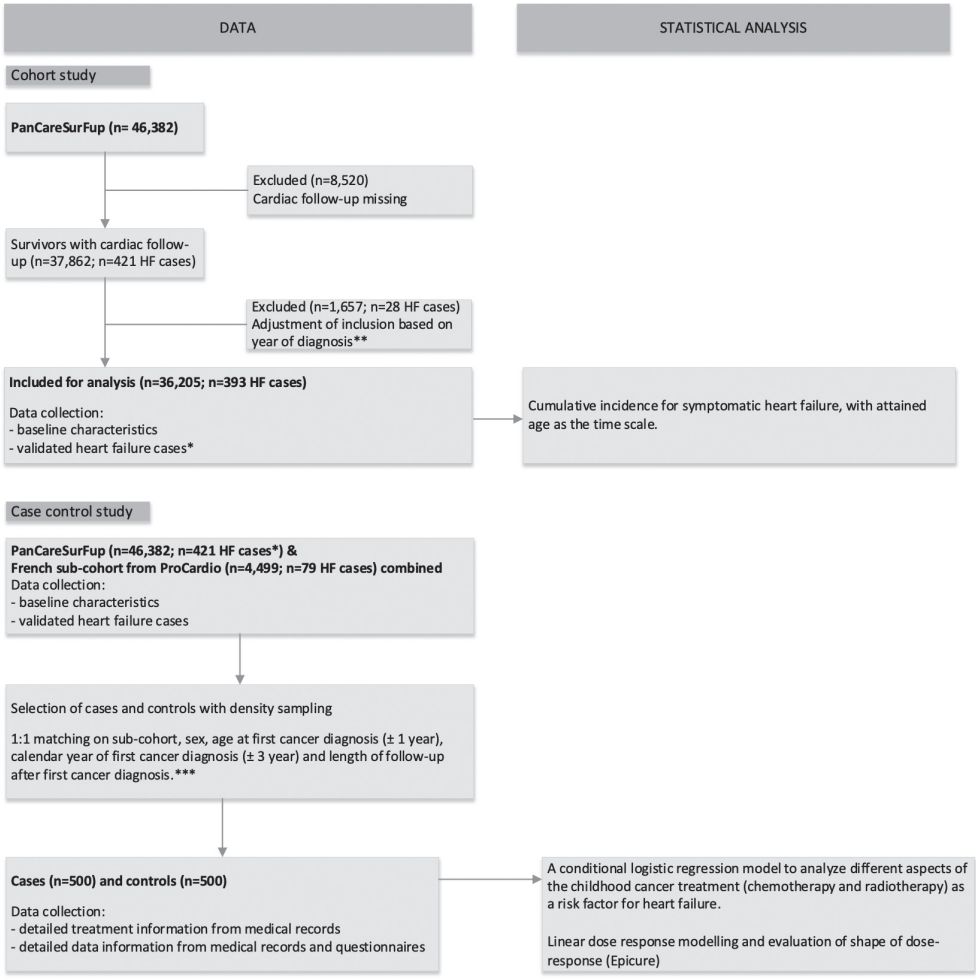
F. Characteristics of survivors included in the cohort study

G. Cumulative incidence – additional analysis

H. Characteristics of survivors included in the cohort study by sub-cohort

I. Multivariable logistic conditional regression – additional analysis

A. Flowchart of the participants, data collection and statistical analysis



* including the survivors from the UK sub-cohort who were identified by the ProCardio project.

**based on adjustment of end date of study to have >80% completeness of follow-up for all included survivors.

*** we could match 487 cases with a control by using these criteria. For a few cases we needed to relax the criterion for calendar year (n=1), age at diagnosis (n=10) or both (n=2).

B. Inclusion criteria per sub-cohort

Sub-cohort	Type of cohort (≥5 year survivors)	Number of childhood cancer survivors in cohort	Age at primary cancer diagnosis	Type of malignancy	Period of primary cancer diagnosis
PanCareSurFup					
France	Hospital data (5 paediatric oncology centres), clinical trials, and cancer registry	3,171	<21 years	Solid tumours	1940–1986
Hungary	Hospital data, clinical trials, and nationwide cancer registry	5,162	<18 years	All, including benign CNS tumours	1971–2008
Italy – hospital based	Nationwide cancer registry	3,004	<15 years	All	1960–2008
Italy – population based	CCRP (Childhood Cancer Registry of Piedmont)	5,003	<18 years	All	1967–2009
The Netherlands	DCCSS LATER (Dutch Childhood Oncology group Long-term effects) registry based on Nationwide hospital- based cohorts	6,087	<18 years	All	1964–2001
Slovenia	Nationwide Slovenian cancer registry, follow-up clinic	1,256	<16 years	All	1961–2002
Switzerland	Nationwide Swiss Childhood Cancer Registry	4,718	<21 years	All, and LCH	1964–2005
United Kingdom	Nationwide cancer registration	17,981*	<15 years	All	1940–1991
ProCardio					
France	Hospital data (5 paediatric oncology centres), clinical trials, and cancer registry	4,499**	<21 years	Solid tumours	1940-2000
United Kingdom	Nationwide cancer registration	17,981*	<15 years	All	1940–1991

* The populations are the same but, related to available funding, PanCareSurFup evaluated survivors for heart failure up to 31/12/2002 and ProCardio evaluated survivors for heart failure after 31/12/2002.

** This is an extension of the French sub-cohort: including those diagnosed 1940 to 2000 and those who had not yet been previously included in PanCareSurFup.

CNS = central nervous system; LHC= Langerhans Cell Histiocytosis

C. Definition of symptomatic heart failure

Grade 3	Grade 4	Grade 5
Symptomatic heart failure responsive to intervention, or left ventricular ejection fraction <40-20%, or shortening fraction <15%	Refractory heart failure or poorly controlled; left ventricular ejection fraction <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated; life threatening consequences heart failure	Death due to heart failure

D. Overview of analysed chemotherapy groups

Category	Included agents	Dose calculation
Anthracyclines	Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone	Equivalent dose (1,2)
Alkylating agents	Cyclofosfamide, Ifosfamide, Busulphan	Equivalent dose (3)
Antimetabolites	Methotrexate, Cytarabine, Fluorouracil	1:1
Epipodophyllotoxins	Etoposide, Teniposide	1:1
Vinca-alkaloids	Vinblastine, Vindesine, Vincristine	1:1
Platinum agents	Cisplatin, Carboplatin	1:1

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E. Completeness of cardiac follow-up in ≥5-year survivors from the PanCareSurFup cardiac study

Sub-cohort	Original cohorts				Adjusted cohorts		
	Inclusion based on years at diagnosis	Original cohort (n)	Survivors with cardiac follow-up (n)	Survivors with cardiac follow-up (% of the original cohort)	Adjustment of end date (year) of the study *	Adjustment of inclusion based on years of diagnosis †	Survivors with cardiac follow-up after adjustment inclusion (n)
France	1940-1986	3,171	3,143	99.1%	2006	no adjustment	3,143
Hungary	1971-2008	5,162	4,883	71.3%	2006	1971-2001	3,680
Italy-Population based	1967-2009	5,003	1,544	30.8%	2010	1967-2005	1,541
Italy-Hospital based	1960-2008	3,004	1,569	52.2%	2012	1960-2007	1,569
Netherlands	1964-2001	6,087	5,185	85.2%	2012	no adjustment	5,185
Slovenia	1961-2002	1,256	1,147	91.3%	2013	no adjustment	1,147
Switzerland	1964-2005	4,718	3,627	67.3%	2007	1964-2002	3,176
United Kingdom	1940-1991	17,981	16,764	93.2%	2012	no adjustment	16,764
Total		**46,382**	**37,862**	**78.1%**			**36,205**

* survivor with cardiac follow-up > 80% in every sub-cohort

† years at diagnosis; to exclude <5 years survivor

F. Characteristics of survivors included in the cohort study

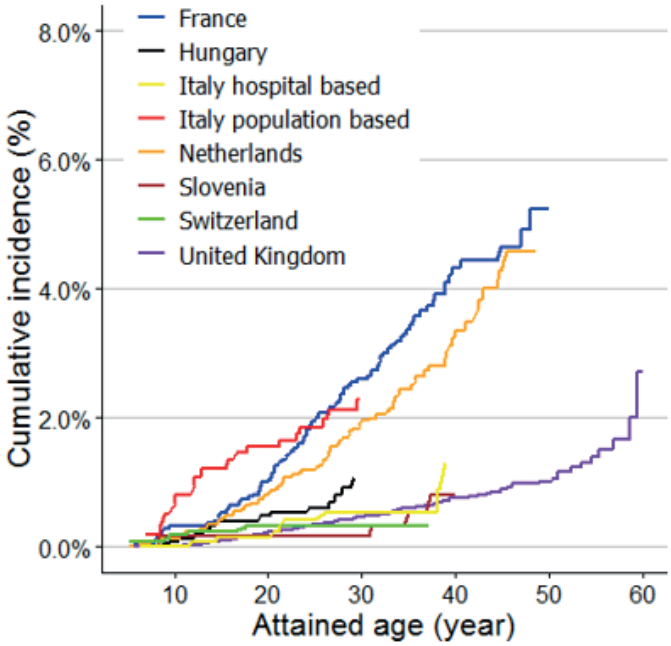
Patient and cancer characteristics of the survivors included in the adjusted PanCareSurFup cohort

	Cardiac follow-up cohort (n=36,205)	Heart failure cases (n=393)	Cardiac follow-up missing (n=8,520)
	n (%)	n (%)	n (%)
Patient characteristics			
Sub-cohort			
France	3,143 (8.7)	99 (25.2)	28 (0.3)
Hungary	3,680 (10.2)	20 (5.1)	279 (3.3)
Italy – population based	1,541 (4.3)	22 (5.6)	3449 (40.5)
Italy – hospital based	1,569 (4.3)	10 (2.5)	1435 (16.8)
The Netherlands	5,185 (14.3)	97 (24.7)	902 (10.6)
Slovenia	1,147 (3.2)	4 (1.0)	109 (1.3)
Switzerland	3,176 (8.8)	8 (2.0)	1091 (12.8)
United Kingdom	16,764 (46.3)	133 (33.8)	1217 (14.3)
Sex			
Female	16,322 (45.1)	171 (43.5)	3733 (43.8)
Age at diagnosis (yr) median (IQR)	*5.8 (2.7-11.0)*	*5.6 (2.7 - 10.8)*	*7.4 (3.2-13.1)*
0 - <5	16,313 (44.6)	181 (46.1)	3194 (37.5)
5 - <10	9,400 (26.0)	100 (25.4)	2006 (23.5)
10 - <15	8,785 (24.3)	96 (24.4)	2136 (25.1)
≥15	1,889 (5.2)	16 (4.1)	1184 (13.9)
Cancer characteristics			
Primary childhood cancer			
Leukemia	9,775 (27.0)	79 (20.1)	2262 (26.5)
Lymphoma	5,587 (15.4)	102 (26.0)	1299 (15.2)
Central nervous system tumour	6,836 (18.9)	12 (3.0)	1752 (20.6)
Bone and soft tissue sarcoma	4,270 (11.8)	98 (24.9)	971(11.4)
Other tumour	9,737 (26.9)	102 (26.0)	2236 (26.2)
Calendar year of diagnosis			
<1980	12,609 (34.8)	158 (40.2)	2519 (29.6)
1980 - <1990	12,660 (35.0)	169 (43.0)	1981 (23.3)
1990-2008	10,936 (30.2)	66 (16.8)	4020 (47.2)
Overall treatment modality			
Surgery only	3,968 (11.0)	9 (2.3)	1150 (13.5)
Chemotherapy ± surgery	7,812 (21.5)	104 (26.5)	2330 (27.3)
Radiotherapy ± surgery	4,810 (13.3)	29 (7.4)	538 (6.3)
Chemotherapy and Radiotherapy ± surgery	11,923 (33.0)	189 (48.1)	1784 (20.9)
No therapy	247 (0.7)	0 (0)	168 (2.0)
Missing	7,445 (20.5)	62 (15.8)	2550 (29.9)
Follow-up			
Vital Status			
Alive	30,761 (85.0)	232 (59.0)	
Deceased	5,444 (15.0)	161 (41)	

	Cardiac follow-up cohort (n=36,205)	Heart failure cases (n=393)	Cardiac follow-up missing (n=8,520)
	n (%)	n (%)	n (%)
Attained age (yr) median (min-max)	*29.7 (5.1-79.8)*	*24.6 (5.3-73.3)*	
<15	2,954 (8.2)	67 (17.0)	
15 - <25	9,068 (25.0)	133 (33.8)	
25 - <35	11,129 (30.7)	105 (26.7)	
35 - <45	8,261 (22.8)	61 (15.5)	
45 - <55	3,464 (9.6)	15 (3.8)	
≥55	1,329 (3.7)	12 (3.1)	
Follow-up duration from primary cancer diagnosis (yr) median (min-max)	*23.0 (5.0-72.5)*	*18.7 (5.0-62.5)*	
>5 - <10	5,205 (14.4)	73 (18.6)	
10 - <20	9,229 (25.5)	145 (36.9)	
20 - <30	11,616 (32.1)	117 (29.8)	
30 - <40	6,688 (18.5)	40 (10.2)	
≥40	3,467 (9.6)	18 (4.6)	
Cardiac events			
Any validated symptomatic cardiac event			
Yes, only 1	749 (2.1)		
Yes, more than 1	138 (0.3)		
No	35,318 (97.6)		
Heart failure			
Grade 3		162 (41.2)	
Grade 4		99 (25.2)	
Grade 5		132 (33.6)	

IQR=interquartile range; min=minimum; max=maximum; N=number; yr= year

G. Cumulative incidence – additional analysis



N at risk France	3143	3072	2713	1781	667	145	14
N at risk Hungary	3680	3431	1939	507	26	0	0
N at risk Italy (hospital)	1569	1533	1185	547	192	17	1
N at risk Italy (population)	1541	1484	1084	489	84	3	0
N at risk Netherlands	5185	5100	3938	2095	689	100	8
N at risk Slovenia	1147	1124	956	568	245	46	2
N at risk Switzerland	3176	2945	1775	606	113	8	0
N at risk United Kingdom	16764	16474	14866	11211	6097	2203	640

Figure**.** Cumulative incidence of heart failure per sub-cohort with attained age as time scale.

H. Characteristics of survivors included in the cohort study by sub-cohort

Median (IQR)	France (n=3.143)	Hungary (n=3.680)	Italy – population based (n=1.514)	Italy – hospital based (n=1.569)	Netherlands (n=5.185)	Slovenia (n=1.147)	Switzerland (n=3.176)	United Kingdom (n=16.764)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Female sex	1.410 (45)	1.620 (44)	735 (48)	726 (46)	2.300 (44)	505 (44)	1.410 (44)	7.625 (46)
Age at childhood cancer diagnosis (yrs)*	*5 (2-10)*	*6 (3-11)*	*11 (4-17)*	*6 (3-10)*	*6 (3-11)*	*8 (3-13)*	*6 (3-12)*	*6 (3-10)*
0 - <5	1.628 (52)	1.607 (44)	430 (28)	693 (44)	2.342 (45)	418 (36)	1.316 (41)	7.697 (46)
5 - <10	747 (24)	1.005 (27)	280 (18)	453 (29)	1.411 (27)	259 (23)	766 (24)	4.479 (27)
10 - <15	663 (21)	852 (23)	290 (19)	341 (22)	1.111 (21)	299 (26)	676 (21)	4.553 (27)
≥15	105 (3)	216 (6)	541 (35)	82 (5)	321 (6)	171 (15)	418 (13)	35 (0.2)
Calendar year of diagnosis	*1977 (1971-1981)*	*1991 (1984-1996)*	*1996 (1991-2000)*	*1993 (1985-1998)*	*1990 (1982-1996)*	*1988 (1980-1996)*	*1992 (1985 -1997)*	*1979 (1971-1986)*
<1980	2.054 (65)	366 (10)	27 (2)	227 (15)	903 (17)	267 (23)	322 (10)	8.443 (50)
1980 - <1990	1.089 (35)	1.281 (35)	259 (17)	346 (22)	1.623 (31)	348 (30)	990 (31)	6.725 (40)
1990-2008	0 (0)	2.033 (55)	1.255 (81)	996 (64)	2.659 (51)	532 (46)	1.864 (59)	1.597 (10)
Attained age (yrs)	*33 (25-41)*	*24 (18-30)*	*25 (19-32)*	*27 (20-34)*	*28 (21-35)*	*30 (22-38)*	*22 (17-28)*	*35 (27-44)*
<15	199 (6)	463 (13)	226 (15)	161 (10)	404 (8)	79 (7)	489 (15)	933 (6)
15 - <25	568 (18)	1.588 (43)	536 (35)	527 (34)	1.682 (32)	291 (25)	1.532 (48)	2.344 (14)
25 - <35	1.026 (33)	1.117 (30)	538 (35)	515 (33)	1.778 (34)	372 (32)	864 (27)	4.919 (29)
35 - <45	929 (30)	472 (13)	237 (15)	285 (18)	1.026 (20)	280 (24)	247 (8)	4.785 (29)
45 - <55	343 (11)	39 (1)	4 (0.3)	74 (5)	258 (5)	112 (10)	43 (1)	2.591 (16)
≥55	78 (3)	1 (0.01)	0 (0)	7 (0.4)	37 (1)	13 (1)	1 (0.01)	1.192 (7)
Vital status								
Alive (no HF)	2.520 (80)	3.412 (93)	1.441 (94)	1.466 (93)	4.519 (85)	978 (85)	2.990 (94)	13.159 (79)
HF grade 3	49 (2)	7 (0.2)	8 (0.5)	4 (0.3)	47 (0.9)	2 (0.2)	3 (0.1)	42 (0.3)
HF grade 4	25 (0.8)	5 (0.1)	11 (0.7)	1 (0.1)	28 (0.5)	0 (0)	1 (0.001)	28 (0.2)
HF grade 5	25 (0.8)	8 (0.2)	3 (0.2)	5 (0.3)	22 (0.4)	2 (0.2)	4 (0.1)	63 (0.4)
Deceased (no HF)	524 (17)	248 (7)	78 (5)	93 (6)	569 (11)	165 (14)	178 (6)	3.472 (21)

Median (IQR)	France (n=3.143)	Hungary (n=3.680)	Italy – population based (n=1.514)	Italy – hospital based (n=1.569)	Netherlands (n=5.185)	Slovenia (n=1.147)	Switzerland (n=3.176)	United Kingdom (n=16.764)
Treatment per cancer type								
Leukaemia	*0 (0)*	*1135 (31)*	*294 (19)*	*674 (43)*	*1.798 (35)*	*263 (23)*	*1.044 (33)*	*4.456 (27)*
Chemo only		269 (24)	46 (16)	353 (52)	1.124 (63)	104 (40)	689 (66)	315 (7)
RT only		0 (0)	0 (0)	0 (0)	1 (0.1)	3 (1)	0 (0)	4 (0.1)
Chemo and RT		733 (64)	16 (6)	281 (42)	648 (36)	150 (57)	336 (32)	2970 (65)
Missing		132 (12)	231 (79)	39 (6)	19 (1)	1 (1)	15 (1)	1.278 (28)
Lymphoma	*561(18)*	*586 (16)*	*275 (18)*	*290 (19)*	*847 (16)*	*241 (21)*	*670 (21)*	*2.117 (13)*
Chemo only	164 (29)	133 (23)	7 (3)	91 (31)	516 (61)	56 (32)	266 (40)	273 (13)
RT only	58 (10)	4 (1)	1 (0.4)	14 (5)	32 (4)	38 (16)	26 (4)	593 (28)
Chemo and RT	332 (59)	411 (70)	13 (5)	146 (50)	289 (34)	138 (57)	279 (42)	473 (22)
Missing	0 (0)	34 (6)	254 (92)	19 (7)	8 (1)	0 (0)	51 (8)	730 (35)
Bone and soft tissue sarcoma	*598 (19)*	*391 (11)*	*293 (19)*	*150 (10)*	*700 (14)*	*123 (11)*	*300 (9)*	*1.715 (10)*
Chemo only	146 (24)	204 (52)	9 (3)	52 (35)	332 (47)	51 (42)	142 (47)	217 (13)
RT only	95 (16)	8 (2)	0 (0)	0 (0)	43 (6)	8 (7)	4 (1)	284 (17)
Chemo and RT	292 (49)	128 (33)	8 (3)	72 (48)	268 (38)	38 (31)	125 (42)	402 (23)
Missing	0 (0)	14 (4)	275 (94)	12 (8)	7 (1)	0 0)	15 (5)	526 (31)
Central nervous system	*448 (14)*	*723 (20)*	*232 (15)*	*153 (10)*	*701 (14)*	*211 (18)*	*469 (15)*	*3.899 (23)*
Other tumours	*1.536 (49)*	*844 (23)*	*447 (29)*	*302 (19)*	*1.139 (22)*	*309 (27)*	*693 (22)*	*4.466 (27)*

I. Multivariable conditional logistic regression – additional analyses

Table 1. Likelihood ratio test (LRT) for linear trend in continuous exposure to specific types of chemotherapy *

	Deviance	LRT p-value
Model 1		
Anthracycline dose category + mean heart RT dose category	-159.78	
Anthracycline dose category + mean heart RT dose category + alkylating agents dose (continuous)	-159.70	0.70
Model 2		
Anthracycline dose category + mean heart RT dose category	-159.88	
Anthracycline dose category + mean heart RT dose category + antimetabolites dose (continuous)	-158.78	0.14
Model 3		
Anthracycline dose category + mean heart RT dose category	-157.72	
Anthracycline dose category + mean heart RT dose category + epipodophyllotoxins dose (continuous)	-156.75	0.16
Model 4		
Anthracycline dose category + mean heart RT dose category	-146.10	
Anthracycline dose category + mean heart RT dose category + vinca-alkaloids dose (continuous)	-146.08	0.87

***** It was not possible to satisfactorily assess the independent effect of platinum compunds because 84% of cases exposed to platinum compounds were also exposed to ≥ 250 mg/m^2 of cumulative anthracycline dose.

LLR= likelihood ratio test; p= p-value; RT= radiotherapy

Table 2. Multivariable conditional logistic regression model of grade 3-5 heart failure by cancer treatment variables

	Dose	Cases* (n)	Controls (n)	OR (95%CI)	p-value
Anthracyclines (mg/m²)	0	135	321	Ref	-
	>0 - <100	9	22	2.4 (0.7-8.1)	0.2
	100 - <200	36	49	5.0 (2.2-11.0)	<0.0001
	200 - <300	55	38	8.1 (3.8-17.0)	<0.0001
	300 - <400	73	37	15.9 (7.5-33.6)	<0.0001
	≥ 400	125	19	69.5 (27.6-175)	<0.0001
	Missing[1]	67	14		p_{trend} <0.0001
Mean heart RT (Gray)	0	166	215	Ref	-
	>0 - <2	116	170	1.3 (0.7-2.2)	0.4
	2 - <5	22	25	1.8 (0.8-4.4)	0.2
	5 - <10	36	11	8.2 (2.8-23.1)	<0.0001
	10 - <20	61	32	8.6 (3.8-19.3)	<0.0001
	20 - <30	50	26	9.8 (4.2-22.9)	<0.0001
	≥30	41	14	17.0 (6.0-48.4)	<0.0001
	Missing[2]	8	7		p_{trend} <0.0001

*matching variables: sub-cohort, sex, age at first cancer diagnosis (± 1 year), calendar year of first cancer diagnosis (± 3 year) and length of follow-up after first cancer diagnosis.

[1] n=9 cases, n=2 controls unknown whether received anthracyclines versus n=58 cases, n=12 controls received anthracyclines but dose unknown

[2] n=1 cases, n=2 controls unknown whether received radiotherapy versus n=7 cases, n=5 controls exposed but dose on heart unknown

CI=confidence interval; n=number; OR=odds ratio; RT=radiotherapy; Ref=reference group

Table 3. Multivariable conditional logistic regression of grade 3-5 heart failure including interaction terms of treatment and/or age at diagnosis

	OR (95%CI)	p-value
Model A		
Anthracycline dose* (mg/m²)		
0	Ref	-
>0 - <100	3.0 (0.9-9.2)	0.062
100 - <200	5.0 (2.3-10.8)	<0.0001
200 - <300	7.7 (3.8-15.9)	<0.0001
300 - <400	16.1 (7.6-34.2)	<0.0001
≥ 400	59.5 (24.8-143.2)	<0.0001
Mean heart RT dose continuous (per 10 Gray)	2.5 (2.0-3.2)	<0.0001
p-value for interaction [a]		*0.2*
Model B		
Anthracycline dose* (mg/m²)		
0	Ref	-
>0 - <100	2.9 (0.9-9.1)	0.076
100 - <200	5.4 (2.4-11.9)	<0.0001
200 - <300	8.2 (3.9-17.1)	<0.0001
300 - <400	15.9 (7.4-33.9)	<0.0001
≥ 400	74.4 (29.1-190.3)	<0.0001
Mean heart RT dose continuous (per 10 Gray)	2.5 (1.9-3.2)	<0.0001
Age at diagnosis (years)		
0 - <5	Ref	-
5 - <10	4.7 (0.8-28.4)	0.095
≥10	0.5 (0.04-5.8)	0.565
p-value for interaction anthracycline dose X age at diagnosis [b]		*0.836*
p-value for interaction mean heart RT dose X age at diagnosis [c]		*0.179*

***** Anthracycline dose was added as categorical variable because the dose-response relationship was non-linear.

[a] P-value was calculated using a likelihood ratio test (comparison of two models; 1) including anthracycline dose and mean heart RT dose versus 2) adding an interaction term of anthracycline dose and mean heart RT dose to the first model).

[b] P-value was calculated using a likelihood ratio test (comparison of two models; 1) including anthracycline dose, mean heart RT dose and age at diagnosis versus 2) adding an interaction term of anthracycline dose and age at diagnosis to the first model).

[c] P-value was calculated using a likelihood ratio test (comparison of two models; 1) including anthracycline dose, mean heart RT dose and age at diagnosis versus 2) adding an interaction term of mean whole RT dose and age at diagnosis to the first model).

Table 4. Characteristics of the survivors included in the case-control study who have only been exposed to heart RT and not to anthracyclines

		Cases 108 n (%)	Controls 189 n (%)
Sex*	Female	44 (41)	86 (46)
Sub-cohort*	United Kingdom	29 (27)	46 (24)
	France	63 (58)	100 (53)
	Netherlands	5 (5)	27 (14)
	Italy	3 (3)	5 (3)
	Switzerland	1 (1)	4 (2)
	Hungary	5 (5)	4 (2)
	Slovenia	2 (2)	3 (2)
Type of childhood cancer	Leukemias, myeloproliferative diseases and myelodysplastic diseases	3 (3)	14 (7)
	Lymphomas and reticulo endothelial neoplasms	52 (48)	43 (23)
	CNS and miscellaneous intracranial and intraspinal neoplasms	6 (6)	55 (29)
	Neuroblastoma and other peripheral nervous cell tumors	8 (7)	15 (8)
	Retinoblastoma	2 (2)	3 (2)
	Renal tumors	19 (18)	34 (18)
	Bone tumors	2 (2)	5 (3)
	Soft tissue and other extraosseous sarcomas	9 (8)	14 (7)
	Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	3 (3)	4 (2)
	Others	4 (4)	2 (1)
Age at childhood cancer diagnosis (yrs)*	*Median (IQR)*	*7.6 (4.1-12.2)*	*6.9 (3.8-11.5)*
	0 - <5	32 (30)	65 (34)
	5 - <10	34 (32)	55 (29)
	10 - <15	34 (32)	59 (31)
	≥15	8 (7)	10 (5)
Calendar year of diagnosis*	<1980	84 (78)	128 (68)
	1980 - <1990	23 (21)	46 (24)
	1990-2008	1 (1)	15 (8)
Attained age (yrs)	*Median (min-max)*	*37.7 (13-73)*	*31.7 (8.2-63.2)*
	<15	3 (3)	15 (8)
	15 - <25	13 (12)	46 (24)
	25 - <35	30 (28)	57 (30)
	35 - <45	29 (27)	46 (24)
	45 - <55	22 (20)	18 (10)
	≥55	11 (10)	7 (4)
Mean heart RT dose (Gy)	*Median (IQR)*	*20.9 (3.9-30.5)*	*1.2 (0.3-16.0)*
	>0 - <5	28 (26)	122 (65)
	5 - <15	15 (14)	19 (10)
	15 - <35	50 (46)	43 (23)
	≥35	15 (14)	5 (3)

		Cases 108 n (%)	Controls 189 n (%)
Maximum heart RT dose (Gy)	*Median (IQR)*	*31 (13.3-41.8)*	*3.6 (0.8-30.0)*
	>0 - <5	16 (15)	102 (54)
	5 - <15	12 (11)	16 (9)
	15 - <35	30 (29)	38 (20)
	≥35	50 (46)	33 (18)
Grade of validated heart failure	Grade 3	30 (28)	0 (0)
	Grade 4	22 (20)	0 (0)
	Grade 5	56 (52)	0 (0)

*Matching variable to select controls (ratio 1:1): on sub-cohort, sex, age at first cancer diagnosis (± 1 year), calendar year of first cancer diagnosis (± 3 year) and length of follow-up.

CNS= central nervous system; Gy=Gray; IQR=interquartile range; min=minimum; max=maximum; n.a.= not applicable; RT=radiotherapy; yrs= years;

Table 5. Characteristics of the survivors included in the case-control study who have been exposed to a mean heart RT dose of 5 - <15 Gray, divided by the maximum heart RT dose

	Cases (n=55) n (%)	Controls (n=25) n (%)
Maximum heart RT dose 5-<15 Gray	**28 (51)**	**5 (20)**
Volume of the heart exposed		
10 - <50% received 5 - <15 Gray	1	0
≥ 50% received 5 - <15 Gray	27	5
Type of childhood cancer		
Leukemia	19	1
Lymphoma	6	1
CNS	0	1
Neuroblastoma	1	2
Renal tumors	1	0
Germ cell tumors	1	0
Calendar year of diagnosis		
<1980	4	2
1980 - <1990	13	3
1990-2008	11	0
Anthracycline dose (mg/m^2)		
No	5	2
>0 - <100	4	0
100 - <250	4	1
≥ 250	7	2
Unknown	8	0
Maximum heart RT dose ≥15 Gray	**27 (49)**	**20 (80)**
Volume of the heart exposed		
>0 - <10% received ≥15 Gray	10	3
10 - <50% received ≥15 Gray	16	14
≥ 50% received ≥15 Gray	1	3
Type of childhood cancer		
Leukemia	1	1
Lymphoma	6	5
CNS	2	4
Neuroblastoma	3	2
Renal tumors	6	6
Bone tumors	2	1
Soft tissue tumors	5	0
Germ cell tumors	1	0
Others	1	1
Calendar year of diagnosis		
<1980	13	13
1980 - <1990	12	7
1990-2008	2	0
Anthracycline dose (mg/m^2)		
No	10	17
>0 - <100	0	0
100 - <250	2	1
≥ 250	11	1
Unknown	4	1

n = number; RT=radiotherapy

Table 6. Multivariable conditional logistic regression models[1] of grade 3-5 heart failure by volume of the heart exposed to low or high RT doses

	Volume of the heart (%)	Cases* (n)	Controls (n)	OR (95%CI)	p-value
≥ 5 Gy	No RT	166	215	Ref	-
	0 - <10	121	180	1.3 (0.8-2.2)	0.3
	10 - <50	29	21	3.1 (1.3-7.4)	0.01
	50 - <90	49	28	6.2 (2.6-14.6)	<0.0001
	≥90	127	49	11.9 (6.0-23.9)	<0.0001
	Missing[2]	8	7		
≥ 10 Gy	No RT	166	215	Ref	-
	0 - <10	143	192	1.5 (0.9-2.5)	0.1
	10 - <50	32	16	6.7 (2.4-18.3)	0.0002
	50 - <90	59	45	7.0 (3.3-14.8)	<0.0001
	≥90	92	25	14.9 (6.8-32.3)	<0.0001
	Missing[2]	8	7		
≥ 20 Gy	No RT	166	215	Ref	-
	0 - <10	198	213	2.0 (1.2-3.2)	0.01
	10 - <50	28	18	5.4 (2.1-14.4)	0.001
	50 - <90	65	39	9.5 (4.4-20.7)	<0.0001
	≥90	35	8	14.1 (4.6-43.1)	<0.0001
	Missing[2]	8	7		
≥ 30 Gy	No RT	166	215	Ref	-
	0 - <10	245	244	2.2 (1.4-3.6)	0.001
	10 - <50	30	12	10.6 (4.1-27.2)	<0.0001
	50 - <90	38	19	11.9 (4.8-29.6)	<0.0001
	≥90	13	3	18.6 (3.5-100)	0.001
	Missing[2]	8	7		

*matching variables: sub-cohort, sex, age at first cancer diagnosis (± 1 year), calendar year of first cancer diagnosis (± 3 year) and length of follow-up after first cancer diagnosis.

[1] all models were adjusted for cumulative anthracycline dose

[2] n=1 cases, n=2 controls unknown whether received radiotherapy versus n=7 cases, n=5 controls exposed but dose on heart unknown

CI=confidence interval; n=number; OR=odds ratio; RT=radiotherapy; Ref=reference group

Table 7. Investigation of potential nonlinearity in the dose-response of cumulative anthracycline dose and mean heart RT dose

	Deviance	LRT *p*
Model 1 Anthracyclines (per 100 mg/m²)		
Null model	693.15	
Anthracyclines	429.63	<0.0001†
Anthracyclines + anthracyclines quadratic	422.67	0.008‡
Anthracyclines + anthracyclines quadratic + anthracyclines cubic	422.10	0.5‡
Model 2 Mean heart RT (per 10 Gray)		
Null model	693.15	
Radiation	609.53	<0.0001†
Radiation + radiation quadratic	609.46	0.8‡
Radiation + radiation quadratic + radiation cubic	609.38	0.8‡
Model 3 Mean heart RT (per 10 Gray) adjusted for anthracyclines (per 100 mg/m²)		
Null model	693.15	
Radiation	609.53	<0.0001†
Radiation + anthracyclines	354.05	<0.0001[a]
Radiation + anthracyclines + anthracyclines quadratic	343.47	<0.0001[b]

†p-value relative to the null model.

‡p-value relates to likelihood-ratio test resulting from extending the existing model by the additional term. So linear extended to linear-quadratic; linear-quadratic to linear-quadratic-cubic.

[a]P-value relative to the model with linear radiation dose only.

[b]P-value relative to the model with linear radiation and anthracycline dose.

CI=Confidence Interval; EOR=Excess Odds Ratio; LRT=likelihood ratio test

Table 8. Classification of the risk according to the IGHG cardiomyopathy guideline of the cases who fall into the newly identified risk groups

	Risk according to the IGHG cardiomyopathy surveillance guideline		
Newly identified risk groups	**Low risk[1]**	**Moderate to high risk[2]**	**Total**
Mean heart RT 5-15 Gray	17 (31%)	38 (69%)	55
≥50% of the heart exposed to a maximum heart RT dose* of 5-15 Gy	16 (60%)	11 (40%)	27

[1]Anthracycline dose <100 mg/m2 or unclear and maximum heart RT dose* <15 Gy

[2]Anthracycline dose ≥100 mg/m2 and/or maximum heart RT dose* ≥15 Gy

* surrogate of the maximum heart RT dose = prescribed chest RT dose

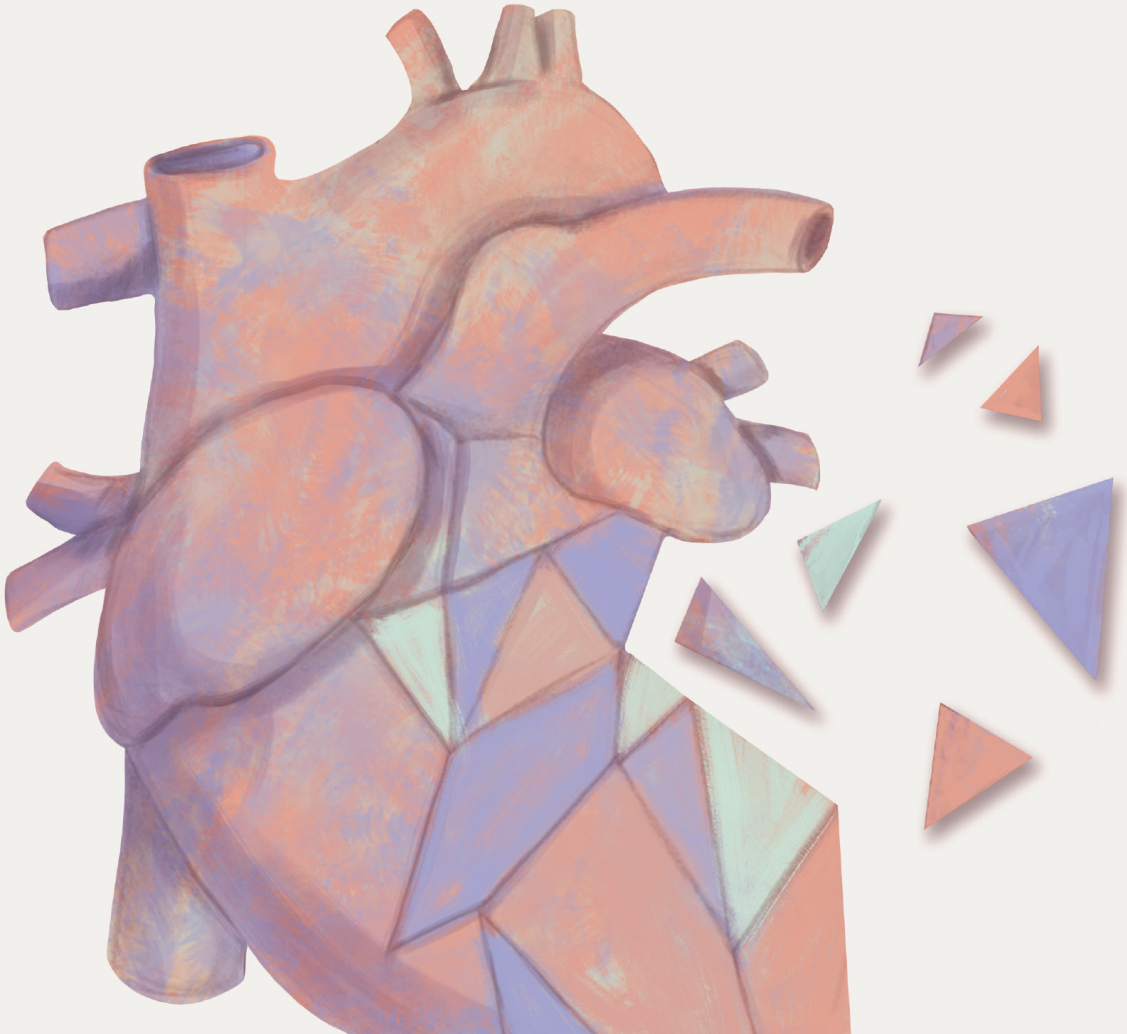
Table 9. Treatment-related characteristics of the cases who received a mean heart RT dose of 5-<15 Gray stratified by the risk groups of the IGHG cardiomyopathy surveillance guideline

	Risk according to the IGHG cardiomyopathy surveillance guideline	
	Low risk[1] n=17	**Moderate to high risk[2] n=38**
Primary cancer diagnosis		
Leukaemia	11 (65)	9 (24)
Lymphoma	4 (23)	8 (21)
Renal tumour	1 (6)	2 (5)
Germ cell tumour	1 (6)	1 (3)
Neuroblastoma	0 (0)	4 (11)
Renal tumour	0 (0)	6 (16)
Bone tumour	0 (0)	2 (5)
Soft tissue sarcoma	0 (0)	5 (13)
Others	0 (0)	1 (3)
Received TBI		
No	8 (47)	31 (82)
Yes	9 (53)	7 (18)
% of the heart that received a maximum* of 5-<15 Gy		
10-50%	1 (6)	0 (0)
≥50%	16 (94)	11 (29)
Maximum dose ≥15 Gy	0 (0)	27 (71)
Anthracycline dose		
No	5 (30)	10 (26)
>0-100 mg/m2	4 (23)	0 (0)
100-<250 mg/m2	0 (0)	6 (16)
≥250 mg/m2	0 (0)	18 (47)
Unknown	8 (47)	4 (11)
Treatment period		
<1980	4 (23)	13 (34)
1980-<1990	10 (59)	15 (40)
1990-2008	3 (18)	10 (26)

[1]Anthracycline dose <100 mg/m2 or unclear and maximum heart RT dose* <15 Gy

[2]Anthracycline dose ≥100 mg/m2 and/or maximum heart RT dose* ≥15 Gy

* surrogate of the maximum heart RT dose = prescribed chest RT dose



CHAPTER 4

Early detection

4.1

ELECTROCARDIOGRAPHIC ABNORMALITIES IN CHILDHOOD CANCER SURVIVORS TREATED WITH CARDIOTOXIC THERAPY: A SYSTEMATIC REVIEW

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Pediatric Blood & Cancer. 2022 Aug;69(8):e29720

ABSTRACT

Purpose – The purpose of this study is to assess the available literature on the prevalence and risk factors of electrocardiographic (ECG) abnormalities after cardiotoxic treatment in childhood cancer survivors (CCS).

Methods – A literature search was performed within MEDLINE, EMBASE and CENTRAL (1966-11/2020) and reference lists of relevant studies. Studies were eligible for inclusion if they reported ECG abnormalities ≥2 years after cancer diagnosis in ≥50 CCS treated with anthracyclines, RT involving the heart region and/or mitoxantrone. Information about population, treatment, outcome and risk factors were extracted and risk of bias was assessed.

Results – Of 934 identified publications, 10 studies were included. Outcome definitions, treatment regimens, follow-up period and risk of bias varied. These ECG abnormalities and prevalences were reported: major (5-23%) and minor (12%) abnormalities according to the Minnesota Code, rhythm abnormalities (0-12%), conduction abnormalities (0.3-7.1%) depolarization abnormalities (0%) and repolarization abnormalities (0-65%). The reported risk factors of ECG abnormalities (2 studies) are male sex, anthracyclines, RT involving the heart region and hypertension, although results were not univocal between studies and abnormalities.

Conclusions – Multiple ECG abnormalities have been described in CCS ≥2 years from diagnosis, some of which can have important implications. Future research is needed to evaluate the exact long-term incidence and risk factors, and to investigate their clinical relevance and relation with cardiac dysfunction or future cardiac events. This could improve cardiac surveillance for CCS.

BACKGROUND

Survival rates of childhood cancer have improved considerably[1]. However, this is accompanied by late treatment related effects including cardiovascular diseases which lead to an increased risk of morbidity and mortality[2,3]. The main causes of cancer therapy related cardiovascular diseases are anthracyclines, mitoxantrone and radiotherapy (RT) involving the heart region[4-6]. Cardiotoxicity in childhood cancer survivors (CCS) may occur as subclinical cardiac dysfunction, heart failure, cardiac ischemia, pericarditis, valvular disease or arrhythmias[7-9]. Thirty years after both anthracycline treatment and radiotherapy, one in eight CCS will develop a serious heart disease [7].

Early detection of cardiotoxicity is an important topic in the field of cardio-oncology. Currently, echocardiography is the cornerstone of surveillance guidelines in CCS[10,11]. In addition, it is recommended to perform an electrocardiogram (ECG) during the first visit (5 years after cancer diagnosis) at the long-term follow-up clinic and when clinically indicated[11,12]. The scientific statement of the American Heart Association from 2013 indicates that the value of repeated testing in CCS may be limited under the assumption that cardiotoxicity and remodeling would precede conduction abnormalities and arrhythmia's[13]. It is important to investigate the added value of other abnormal ECG patterns, including pathologic Q-waves, because a part of the cardiac injury induced by cancer treatment may go unrecognized by echocardiographic surveillance only.

Normal values of ECG parameters and prevalence of ECG abnormalities in the general population have been established[14,15]. The clinical use of ECG examination has been proven for diagnosing acute coronary artery syndromes, intraventricular conduction disturbances and arrhythmias[16,17]. In addition, large studies reflecting the general population have identified certain ECG patterns that are related with future cardiac events[18,19]. Data of MESA (Multi-Ethnic Study of Atherosclerosis) and results in people with increased risk of heart failure demonstrated that there are also several ECG markers including Minnesota Codes associated with heart failure which may be indicative of electrical remodeling[20-22].

Up to now, the precise role and added value of this widely available diagnostic tool in the evaluation of cardiotoxicity in CCS remain unclear. The objective of this systematic review is to assess the available literature on the prevalence and risk factors of ECG abnormalities in CCS exposed to anthracyclines and/or mitoxantrone and/or radiotherapy involving the heart region.

METHODS

Search strategy

We searched databases MEDLINE/PubMed, EMBASE and CENTRAL (Cochrane Central Register of Controlled Trials) with a combination of terms for 'anthracyclines', 'mitoxantrone', 'radiotherapy', 'children'[23] and 'electrocardiography' (Supplemental Table 1). The searches were executed on November 5th, 2020. MEDLINE covers literature from 1966 and EMBASE from 1974 onwards. In addition, we explored the reference lists of included studies and reviews and we asked experts in the field for missing information on potentially eligible studies.

Study selection

Two independent authors performed title and abstract screening to identify studies that potentially meet the inclusion criteria. The same two authors screened the full texts for eligibility. We included original studies in English or Dutch evaluating ≥50 CCS who are treated with cardiotoxic cancer treatment (without concurrent cardio-protective intervention) and had ECG assessment. At least 90% of the study population needed to be diagnosed at age ≤21 years. Cardiotoxic cancer treatment included anthracyclines, mitoxantrone and RT involving the heart region, separately as well as combined. Any electrocardiographic evaluation was suitable for inclusion (eg. standard 12-lead ECG or Holter) but should have been performed ≥2 years after cancer diagnosis in 90% of the eligible patients. The searched outcomes were prevalence of ECG abnormalities (as defined in included studies) or its risk factors derived from multivariate analysis.

Case reports, case series and original reports that did not separate results from eligible and ineligible patients were excluded. In case of duplicate populations with overlapping results, we included the best report (see Supplemental Table 2 for preference order).

Data extraction

The same two independent authors extracted data from each article by using a pre-prepared form. The extracted data included characteristics of the study design, study population (like age, sex), cancer, follow-up and outcome (like QTc prolongation or left bundle branch block).

Risk of bias assessment

The assessment of risk of bias (or internal validity) in observational studies was based on previously described checklists according to evidence-based medicine criteria[24,25] as recommended by Cochrane Childhood Cancer (https://childhoodcancer.cochrane.org/). See Supplemental Table 3 for the definitions of the different risk of bias criteria. The internal validity gives an indication of the bias present in a study and thus how valid the results of a certain study are. It includes the following issues: selection bias, attrition bias, detection bias and, if a risk assessment is performed, confounding. The external validity of a study indicates how well its results can be extrapolated to an individual CCS who received cardiotoxic treatment. It includes the following issues: well-defined study group, well-defined follow-up, well-defined outcome and, if risk assessment was performed, a well-defined analysis. The presence of internal or external validity issues was not a reason to exclude a study from the review.

The discrepancies between the reviewers regarding study selection, data extraction and risk of bias assessment were discussed and resolved; no third party arbitration was needed.

Statistical analysis

We calculated the prevalence of ECG abnormalities as the number of CCS with ECG abnormalities divided by the total number of CCS treated by anthracyclines and/or mitoxantrone and/or RT involving the heart region in the study group in which it was measured. To compute the accompanying 95% confidence interval (CI) we used the Wilson Score Interval method. We would have performed pooling of results if studies were comparable including the definition of ECG abnormalities that was used; this was not the case and therefore we provide descriptive results. In the interpretation of the results the risk of bias in the included studies was taken into account.

RESULTS

Identified studies

Figure 1 presents the flowchart of study selection. The searches yielded 934 unique reports of which 858 were excluded during title/abstract screening. Of the 76 reports that were screened as full text, 11 reports fulfilled all the inclusion criteria for this review[8,26-35]. However, one report[8] was excluded because of overlapping cohorts. The most recent and largest study cohort was chosen[28], making the total number of included reports 10.

Both studies of Pourier et al.[29,30] included CCS who visited the same Late Effects Clinic. We decided to include both studies since the time period between these two studies differ. Still, there might be a certain degree of overlap between these study cohorts if patients visit the clinic every five years.

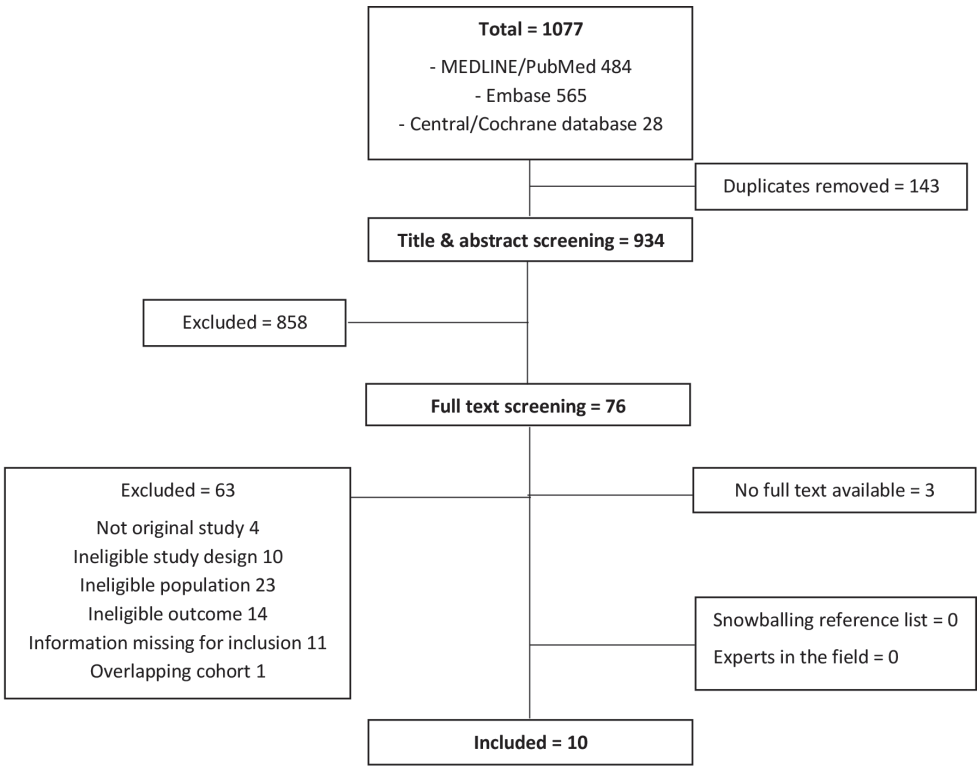

Figure 1. Flowchart study selection

Table 1 provides detailed information about the relevant study cohort (CCS treated with cardiotoxic treatment) that was evaluated in the 10 eligible studies. When a study only reported patient and/or treatment-related characteristics for the overall study cohort (also including CCS who did not receive cardiotoxic treatment), we stated "not mentioned" in the results. In total there were 1116 eligible CCS of whom 1070 had an ECG examination at least two years after diagnosis. We could not include the study of Mulrooney et al.[28] in this number because the information about how many participants received one or more different cardiotoxic treatments was not provided, both in this study and in the previous study[8].

Of the 10 eligible reports, three studies included acute lymphoblastic leukemia survivors only, one study described Hodgkin lymphoma survivors only and in six studies CCS were diagnosed with various cancer types.

All studies included participants who were diagnosed with childhood cancer, however we could only extract age at cancer diagnosis from four studies which ranged from 0 to 21.9 years[29,31,32,34]. Follow-up duration until ECG examination was reported as median which ranged from 6.5-15.3 years or as mean which ranged from 11-21 years. The minimum time after diagnosis or end of treatment of included patients was 4 years; one study did not mention the exact follow-up duration for the eligible CCS[28]. The starting point of the calculated follow-up time was not equal in studies; two studies reported follow-up period as time from cancer diagnosis[27,31], two studies as time from end of treatment[26,35], in six studies the starting point was unclear[28-30,32-34].

The attained aged was provided as median or mean, the median varied between 16.7-21 years of age, the mean varied between 19.7-32 years of age and was not reported for the eligible CCS in two studies[28,35].

Table 1. Characteristics of included studies assessing prevalence of ECG abnormalities in CCS treated with cardiotoxic treatment

1st author, year, country, and period	Design and population	Study cohort[a] (n)	Eligible for review[b] (n (% females))	Definition of subgroups	Age at cancer diagnosis Follow-up duration Age at ECG (years)	Cumulative dose of Anthracycline (mg/m^2 (%))	Cumulative dose of chest RT (Gray, (%))	Cumulative dose of mitoxantrone (mg/m^2 (%))
Caru, 2019, Canada, nm. (27)	Cross-sectional ALL, ANT, ≥ 5years after diagnosis Cardiac exclusion criteria: no	140	Total = 140 (nm) Group I =89 Group II =51	Based on gender, age, time from end treatment and prognostic risk group: Group I = standard risk Group II = high risk	Group I nm mean 15.5 ± 5[c] mean 19.7 ± 4.9 Group II nm mean 17.9 ± 3.4[c] mean 28.3 ± 5.3	Group I DOX mean 66.8 ± 45.8 (100) Group II DOX mean 287.6 ± 68.6 (100)	Group I 0 (100) Group II 0 (100)	Group I 0 (100) Group II 0 (100)
Materazzo, 2017, Italy, nm. (28)	Cross-sectional HL, ANT with(out) RT, ≥ 5years survival Cardiac exclusion criteria: no	83	53 (23)	Unselected asymptomatic group with additional stress echocardiography.	nm mean 21[d] mean 32 ± 4.1	0 (0) DOX 150 (58) DOX 300 (42) *According to the protocol*	nm (89% of the total cohort, dose nm)	0 (100)
Mulrooney, 2017, USA, Nov 2007-Jun. 2014 (29)	Cross-sectional Various cancer types, ANT and/or RT, ≥ 10 years after diagnosis Cardiac exclusion criteria: no	Unclear	Unclear[e] Group I = 1573 Group II = 800	Group I = treated with anthracyclines Group II = exposed to cardiac radiotherapy	nm nm nm	Group I DOX equivalents 1-200 (66) 201-400 (28) >400 (6)	Group II 0.01-19 (59) 20-29 (27) ≥30 (14)	nm *(Included in the DOX equivalent dose (mitoxantrone dose * 4))*
Pourier, 2017, Netherlands, May 2006 – May 2010. (30)	Cross-sectional Various cancer types, ANT with(out) RT, ≥ 5 years after ANT treatment Cardiac exclusion criteria[g]	340	340 (46)		mean 6.9 ± 4.7 mean 14.5 ± 7.4[f] mean 21.4 ± 8.4	Sum of DOX and DAU dose 0 (0) median 180, 30-600 (100)	0 (86) Dose nm (14)	nm

1st author, year, country, and period	Design and population	Study cohort[a] (n)	Eligible for review[b] (n (% females))	Definition of subgroups	Age at cancer diagnosis Follow-up duration Age at ECG (years)	Cumulative dose of Anthracycline (mg/m² (%))	Cumulative dose of chest RT (Gray, (%))	Cumulative dose of mitoxantrone (mg/m² (%))
Pourier, 2015, Netherlands, Feb 2012 – Sept 2012. (31)	Cross-sectional Various cancer types, ANT with(out) RT, ≥ 4.5 years survival Cardiac exclusion criteria[i]	64	57 (nm)		nm (median 5.8, 0.3–17.3[h]) nm (median 8.3, 4.5–34.1[d,h]) nm (median 16.7, 7.2–39.8[h])	nm (0 (0)[h]) nm (median 225, 85–450[h]) *ANT analogue is unclear*	nm (0 (77)[h]) Dose nm	nm
Landier, 2012, USA, Oct 2003 -Nov 2010 (32)	Cross sectional Various cancer types, ANT and/or RT and/or mitox, ≥ 5 years after diagnosis Cardiac exclusion criteria: no	253	248 (47)		median 11.4, 0.3-21.9 median 9.0, 5-35.8[d] median 21.0, 5-53	Median doses 0 (0) DAU 100, 25-500 (nm) DOX 150, 25-500, (nm) EPI 300, 250-600 (nm) IDA 36, 35-108 (nm)	nm	Median 63, 36-135 (nm)
Rajic, 2009, Slovenia, nm. (33)	Cross-sectional ALL, ANT, ≥ 5 years after treatment Cardiac exclusion criteria: no	76	76 (58)		mean 6.3 ± 4.4 mean 19.3 ± 6.3[b] mean 25.8 ± 5.3	0 (0) mean 199 ± 108 (100) *ANT analogue is unclear*	nm	nm
Gupta, 2002, USA, from 1992. (34)	Cross-sectional Various cancer types, ANT with(out) RT, ≥ 4 years survival Cardiac exclusion criteria: no	54	54 (nm) Group I = 39 Group II = 15	Group I = shortening fraction of ≥29% Group II = shortening fraction of <29%	Group I nm mean 11 ± 5[b] mean 22 ± 7 Group II nm mean 13 ± 5[b] mean 26 ± 6	Group I 0 (0) mean 374 ± 147 (100) Group II 0 (0) mean 375 ± 82 (100) *ANT analogue is unclear*	Group I 0 (51) mean 13.5 ± 17 (49) Group II 0 (31) mean 17.3 ± 14 (69)	nm

1st author, year, country, and period	Design and population	Study cohort[a] (n)	Eligible for review[b] (n (% females))	Definition of subgroups	Age at cancer diagnosis Follow-up duration Age at ECG (years)	Cumulative dose of Anthracycline (mg/m² (%))	Cumulative dose of chest RT (Gray, (%))	Cumulative dose of mitoxantrone (mg/m² (%))
Rammeloo, 2000, Netherlands, nm. (35)	Cross-sectional ALL, ANT, ≥ 5 years survival Cardiac exclusion criteria: congenital heart disease	50	50 (58)		median 3.9, 1.3-14.9 median 15.3, 12.7-17.8[b] median 20.1, 14.8-30.0	DAU 0 (0) 100 (100) *Doses according to the protocol*	0 (100)	0 (100)
Schwartz, 1993, USA, 1988-1992. (36)	Cross-sectional Various cancer types, ANT with(out) RT, ≥ 5 years after diagnosis Cardiac exclusion criteria: clinical congestive failure	56	52 (nm)		nm median 6.5, 1.9-16.3[c] nm	DOX equivalents 100 to 199 (11) 200 to 550 (89)	0 (71) Dose nm (29)	nm *Mitoxantrone not included in DOX equivalent*

NOTE: The mean is provided with the standard deviation and the median with the range.

Abbreviations: ALL, acute lymphoblastic leukemia; ANT, anthracyclines; CCS, childhood cancer survivors; DAU, daunorubicin; DOX, doxorubicin; DXZ, dexrazoxane; ECG , electrocardiographic; EPI, epirubicin; HL, Hodgkin Lymphoma; IDA, idarubicin; mg/m², milligrams per squaremeter; mitox, mitoxantrone; n, number; nm, not mentioned; RT, radiotherapy on the heart region.

[a]Relevant study cohort: childhood cancer survivors, ≥2 years from diagnosis, treated with cardiotoxic cancer treatment (anthracyclines, cardiac RT or mitoxantrone), but without dexrazoxane.

[b]For this review: childhood cancer survivors, ≥2 years from diagnosis, treated with cardiotoxic cancer treatment and ECG examination.

[c]Time from end of treatment (years).

[d]Time from cancer diagnosis (years).

[e]The overlap between group I and group II is unclear.

[f]Unknown if since cancer diagnosis or end of therapy.

[g]Abnormal ECG and/or echocardiogram at the start of therapy, incomplete data (ECG and/or echocardiographic) at follow-up, clinical heart failure, cardiac medication, and congenital heart disease.

[h]These are the values of the study cohort[a].

[i]Clinical heart failure (NYHA classes II-IV), a history of cardiovascular disease or chronic renal disease.

CCS received different combinations of cardiotoxic treatments. We were not able to provide detailed information on actual received combinations since frequently not all information was provided. The following results include different types of anthracyclines. Since not all studies provided information about the used anthracycline analogue we chose not to convert the doses by the proposed equivalence ratio[36] and reported the doses as provided by the included study. The actual received cumulative anthracycline dose was reported in eight studies[26,28-33,35] and were provided as mean, median or proportions/range. The cumulative anthracycline doses ranged from 0 to 600 mg/m^2 (median ranged from 36-300 mg/m^2 and mean ranged from 66.8-375 mg/m^2).

Radiotherapy doses were reported in two out of six studies that included CCS treated with RT involving the heart region and ranged from 0.1 to >30 Gray[27-30,33,35]. In 2 studies CCS did not receive RT involving the heart[26,34], while in 2 studies this was unclear[31,32].

In three studies none of the CCS received mitoxantrone[26,27,34], in one study the median dose was 63 mg/m^2 (range 36-135)[31] and in the other six studies information about mitoxantrone was missing [28-30,32,33,35]. In one of these studies mitoxantrone was included in the anthracycline dose[28].

Risk of bias in included studies

See Figure 2 and Supplementary Table 4 for the exact scores per study and the support for the assessments. We have looked both at internal and external validity. Regarding internal validity, the risk of selection bias was low in one study[27], high in one study[33] and unclear in eight studies[26,28-32,34,35]. For most studies the impact of selection bias was unclear due to missing information about the original cohort. The risk of attrition bias was low in nine included studies[27-35] and unclear in one study[26]. The risk of detection bias was low in two studies [29,33] and unclear in the remaining eight studies[26-28,30-32,34,35]. Of the two studies who performed risk factor analysis, both corrected for important prognostic factors leading to a low risk of confounding[28,29].

Concerning external validity, the risk of reporting bias about the study group was low in one study[26] and high in nine studies[27-35]. Radiotherapy doses were not mentioned in four of the six studies that included patients who were exposed to cardiac radiation[27,29,30,35]. In six studies it was unclear whether mitoxantrone was included in the treatment regime[28-30,32,33,35].

The risk of reporting bias about the follow-up was low in eight studies[26,27,29,31-35] and high in two studies [28,30]. The risk of reporting bias about the outcome was low in five studies[26,28,29,33,35] and high in the other five studies[27,30-32,34]. The two studies that conducted multivariable analyses of risk factors, defined their methods well[28,29].

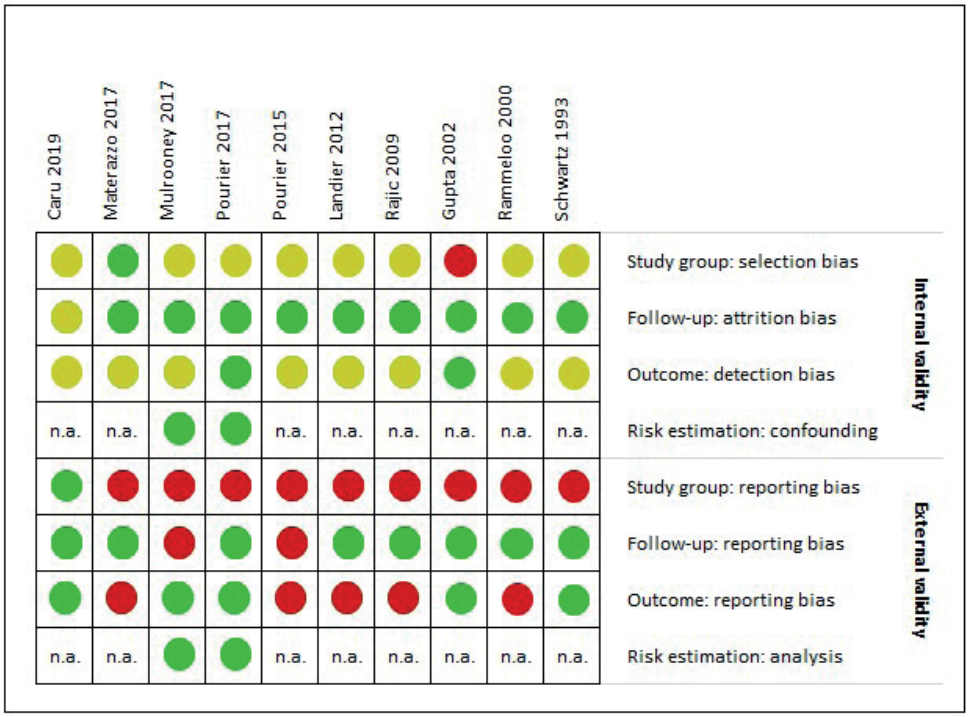

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. na = not applicable

Prevalence of ECG abnormalities

Information on the prevalence of ECG abnormalities is provided in Table 2. Pooling of results was not feasible, due to clinical heterogeneity among the included studies such as treatment, age at diagnosis, attained age, used ECG definitions, differences in inclusion criteria regarding presence of symptomatic heart diseases and differences in the starting point of the calculated follow-up time between the included studies.

Different ECG abnormalities were identified, which could be categorized as ECG abnormalities based on Minnesota Code[37], rhythm disturbances or abnormalities, conduction disorders, depolarization disorders, repolarization disorders and not further

specified. Detailed information about detection method and used definition of the specific ECG abnormalities that are included in the categories are listed per study in Supplementary Table 5.

Two studies reported on ECG abnormalities based on Minnesota Code. The Minnesota Code is an ECG classification system that supports an objective assessment of the ECG. This classification system of "major" and "minor" ECG abnormalities is predominantly used in population studies and covers multiple abnormal patterns such as Q-QS waves, depolarization disorders, high voltages and arrhythmias[37]. In the study of Mulrooney et al. the number of CCS with an ECG was unclear, Pourier et al. evaluated 340 CCS. [28,29]. The prevalence of major ECG abnormalities ranged from 4.7% in a population with anthracycline and RT involving the heart region treatments[29], to 8.6% for those treated with anthracyclines only and 18.3% for those treated with RT involving the heart region only[28]. In the study of Mulrooney et al. the highest prevalence was seen in patients exposed to RT involving the heart region in combination with alkylating agents[28]. Pourier et al. reported a prevalence of minor ECG abnormalities (in the absence of major abnormalities) of 12.4% in asymptomatic CCS[29].

Three studies reported on different rhythm disturbances or abnormalities[26,30,34]; 50 to 340 survivors underwent ECG examination. The prevalence of either supraventricular or ventricular arrhythmias was 0%, this was examined with a 12-lead ECG. The prevalence of ventricular premature contractions on a Holter monitor was 12.1%. The prevalence of bradycardia was 2.6%.

One study described results regarding conduction abnormalities[29]; 340 survivors underwent ECG examination. The prevalence of atrioventricular conduction disorders was 1.2%. The prevalence of all ventricular conduction disorders was 8.5%, which included complete right and left bundle branch block (both 0.3%), incomplete right bundle branch block (7.1%) and left anterior hemi-block (0.9%).

One study in 57 CCS addressed depolarization disorders by evaluating pathologic Q-waves and described a prevalence of 0%[30].

Repolarization disorders were addressed by six studies in total[29-31,33-35]. Five studies evaluated the QTc duration[29,31,33-35]; 50 to 340 underwent ECG examination. One study did not describe the precise method[31], all other studies used Bazett's formula to calculate QTc duration. The prevalence of QTc prolongation defined as >440 milliseconds (exact definition differed slightly between studies) ranged from 0 to 15.4%. One study with 54

survivors also looked at QTc dispersion which is the difference between the longest and the shortest measured QTc interval. Prolonged QTc dispersion may reflect heterogeneous ventricular repolarization[38]. The study reported a prevalence of QTc dispersion prolongation, defined as >65ms, of 64.8%[33]. Two studies focused on ECG patterns suggestive for ischemia, predominantly based on ST-T segment abnormalities[30,34]; the number of survivors with an ECG ranged from 50 to 57. The prevalence was 0% in both studies.

Two studies measured whether T-wave abnormalities were present[29,34]; the number of survivors with an ECG ranged from 50 to 340. The prevalence ranged from 0.3 to 2%.

Non-specific repolarization abnormalities were reported in one study (n=340) with a prevalence of 0.9%[29].

Two studies also reported ECG abnormalities that could not be assigned to one of the above subgroups[29,34]. A QRS axis deviation was reported in 0.3% (n=1 study/340 CCS), left high amplitude R-waves in 4.1% (n=1 study/340 CCS) and micro-voltage in 2% (n=1 study/50 CCS).

Two studies reported the presence of pathological/abnormal signs without a clear definition[27,32].The prevalence of significant ECG abnormalities during or after stress echocardiogram was 0% in one study (53 CCS) and the prevalence of clear conduction disturbances, depolarization, and repolarization changes was 28.9% in the other study (76 CCS).

Risk factors

Two studies performed multivariable risk factor analysis (Table 3). The multivariate analysis of Mulrooney et al. included also CCS who had not received cardiotoxic treatment. Anthracycline treatment (≥300 mg/m^2), RT involving the heart region and hypertension were related to major Minnesota abnormalities and male gender and RT involving the heart region to minor Minnesota abnormalities. The risk for major Minnesota abnormalities associated with 20-30 or >30 Gray of RT involving the heart region only was almost 2-fold and 5-fold higher, respectively, than the risk associated with anthracyclines[28]. In the study of Pourier et al. (2017) only male gender was associated with abnormal ECG patterns (including Minnesota Code and other definitions)[29].

Table 2. Prevalence of ECG abnormalities

ECG abnormality		Prevalence - n/N (%; 95%CI)	Age at ECG examination - years (mean; SD, median; range)	Follow-up time - years (mean; SD, median; range)
Minnesota Code[a]				
Major abnormalities				
Mulrooney, 2017		ANT only: nm/nm (8.5)	nm	nm, ≥ 10 years after diagnosis
		RT only: nm/nm (18.3)	nm	nm, ≥ 10 years after diagnosis
		ANT and RT: nm/nm (17.3)	nm	nm, ≥ 10 years after diagnosis
		ANT and ALK: nm/nm (7.1)	nm	nm, ≥ 10 years after diagnosis
		RT and ALK: nm/nm (23.2)	nm	nm, ≥ 10 years after diagnosis
		RT, ANT and ALK: nm/nm (17.9)	nm	nm, ≥ 10 years after diagnosis
Pourier, 2017		16/340 (4.7; 2.8-7.5)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Only minor abnormalities				
Pourier, 2017		42/340 (12.4; 9.3-16.3)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Rhythm disturbance or abnormalities				
Supraventricular arrhythmias				
Rammeloo, 2000		0/50 (0; 0-0)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
Ventricular arrhythmias				
Rammeloo, 2000		0/50 (0; 0-0)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
Ventricular premature contraction				
Caru, 2019		≥ class III 17/140 (12.1; 7.7-18.6)	[c]	mean 15.5 ± 5 to 17.9 ± 3.4[d]
Bradycardia				
Pourier, 2017		9/340 (2.6; 1.4-5.0)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Conduction disorders				
AV conduction disorders				
Pourier, 2017		4/340 (1.2; 0.5-3.0)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Ventricular conduction disorders				
- LBBB	Pourier, 2017	1/340 (0.3; 0.1-1.6)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
- RBBB	Pourier, 2017	1/340 (0.3; 0.1-1.6)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
- IRBB	Pourier, 2017	24/340 (7.1; 4.8-10.3)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
- LAH	Pourier, 2017	3/340 (0.9; 0.3-2.8)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Depolarization disorders				
Pathological Qs				
Pourier, 2015		0/57 (0; 0-0)	[c]	nm, ≥ 4.5 years survival[c]

ECG abnormality	Prevalence - n/N (%; 95%CI)	Age at ECG examination - years (mean; SD, median; range)	Follow-up time - years (mean; SD, median; range)
Repolarization disorders			
QTc prolongation >450ms males >470ms females			
Landier, 2012	7/248 (2.8; 1.4-5.7)	median 21.0, 5-53	median 9.0, 5-35.8[d]
QTc prolongation >450ms for males and females			
Pourier, 2017	2/340 (0.6; 0.2-2.1)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Gupta, 2002	4/54 (7.4; 2.9-17.6)	[c]	mean 11 ± 5[b] to mean 13 ± 5[b]
Schwartz, 1993	8/52 (15.4; 8.8-27.5)	nm	median 6.5, 1.9-16.3[d]
QTc prolongation >440ms for males and females			
Rammeloo, 2000	0/50 (0; 0-0)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
QTc dispersion prolongation >65ms for males and females			
Gupta, 2002	35/54 (64.8; 51.5-76.2)	[c]	mean 11 ± 5† to mean 13 ± 5[b]
ST abnormalities[e]			
Pourier, 2015	0/57 (0; 0-0)	[c]	nm, ≥ 4.5 years survival[c]
Rammeloo, 2000	0/50 (0; 0-0)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
T wave abnormalities[f]			
Pourier, 2017	1/340 (0.3; 0.1-1.6)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Rammeloo, 2000	1/50 (2; 0.4-10.5)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
Aspecific repolarization abnormality			
Pourier, 2017	3/340 (0.9; 0.3-2.6)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Other ECG abnormalities			
QRS axis deviation			
Pourier, 2017	1/340 (0.3; 0.1-1.6)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Left high-amplitude R waves			
Pourier, 2017	14/340 (4.1; 2.5-6.8)	mean 21.4 ± 8.4	mean 14.5 ± 7.4[b]
Micro-voltage in leads I, II, III			
Rammeloo, 2000	1/50 (2.0; 0.4-10.5)	median 20.1, 14.8-30.0	median 15.3, 12.7-17.8[b]
Abnormal defined as[h]			
Materazzo, 2017	0/53 (0; 0-0)	mean 32 ± 4.1	mean 21[d]
Rajic, 2009	22/76 (28.9; 20.0-40.0)	mean 25.8 ± 5.3	mean 19.3 ± 6.3[b]

Abbreviations: ANT, anthracyclines; ALK, alkylating agents; AV, atrioventricular; CI, confidence interval; ECG, electrocardiography; IVCA, intraventricular conduction abnormalities; IRBBB, incomplete right bundle branch block; LAH, left anterior hemiblock; LBBB, left bundle branch block; msec, millisecond; mV, millivolt; MC, Minnesota Code; PAC, premature atrial complex; PVC, premature ventricular complex; nm, not mentioned; RBBB, right bundle branch block; RT, RT involving the heart region; SD, standard deviation; 24-h, 24 hour.

[a]Prineas RJ, Crow RS, Blackburn H. The Minnesota Code manual of electrocardiographic findings. John Wright-PSG: Littleton, MA. 1982.

[b]Unknown if since cancer diagnosis or end of therapy.

[c]See Table 1 formore details.

[d]End of treatment.

[e]Used definitions according to the related study: Pourier 2015: Signs of myocardial infarction ST-elevation, ST-depression, Rammeloo, 2000: not defined.

[f]Exact definitions according to the related study: Pourier 2017: T-wave items according to the MC (5-3). Rammeloo, 2000: flattened T-waves.

[g]Time from cancer diagnosis.

[h]Exact definitions according to the related study: Materazzo, 2017: Significant ECG abnormalities during or after stress echocardiogram. Rajic, 2009: Clear conduction disturbances, depolarization, and repolarization changes.

Table 3. Multivariate analysis of ECG abnormalities[a]

Mulrooney, 2017	Major Minnesota abnormality Odds ratio (95% CI)	Minor Minnesota abnormality[b] Odds ratio (95% CI)	Pourier, 2017	Abnormal ECG Odds ratio (95% CI)
Gender				
Female	1.0	1.0		
Male	1.2 (0.9-1.5)	1.6 (1.4-1.9)	Male gender (vs female)	3.00 (1.68–5.37)
Race				
White	1.0	1.0		
Black	1.4 (0.9-2.0)	1.3 (0.9-1.6)		
Other	0.9 (0.3-2.9)	0.9 (0.5-1.7)		
Body mass index (kg/m²)	0.9 (0.9-1.0)	0.9 (0.9-1.0)		
Age at diagnosis[c] (y)	0.9 (0.9-1.0)	0.9 (0.9-1.0)	Age at diagnosis (y)[c]	1.02 (0.96–1.08)
Age at evaluation (y)			Follow-up duration (y)[c]	0.99 (0.95–1.02)
18-29	1.0	1.0		
30-39	1.1 (0.8-1.5)	0.9 (0.7-1.1)		
40-49	1.3 (0.9-2.0)	1.2 (0.9-1.6)		
≥ 50	1.9 (0.9-3.7)	1.7 (0.8-3.4)		
Anthracycline (mg/m²)			Cumulative anthracycline dose (≥300 vs. <300mg/m2)	0.86 (0.63–1.18)
None	1.0	1.0		
1-300	1.3 (0.9-1.8)	1.0 (0.8-1.3)		
≥300	1.7 (1.1-2.5)	1.1 (0.8-1.5)		
Alkylating agents (mg/m²)				
None	NE	1.0		
1-9000		1.1 (0.9-1.3)		
≥9000		1.3 (1.0-1.6)		
Cardiac radiation (cGy)			Mediastinal radiation[d] (Gy)	0.60 (0.27–1.37)
None	1.0	1.0		
1-1999	2.1 (1.5-2.9)	1.4 (1.1-1.8)		
2000-2999	2.6 (1.6-3.9)	1.7 (1.2-2.4)		
≥3000	10.5 (6.5-16.9)	4.9 (2.1-11.7)		
Hypertension				
No	1.0	1.0		
Yes	1.6 (1.2-2.1)	1.3 (1.0-1.6)		
Smoking				
No	1.0	1.0		
Yes	1.1 (0.8-1.4)	1.2 (0.9-1.4)		
Dyslipidemia				
No	1.0	1.0		
Yes	1.0 (0.8-1.4)	1.0 (0.8-1.2)		
Diabetes				
No	1.0	1.0		
Yes	1.4 (0.9-2.2)	1.0 (0.7-1.5)		

Abbreviations: cGY, centigray; CI, confidence interval; kg/m^2, kilograms per square meter; mg/m^2, milligrams per square meter; NE, not estimated; OR, odds ratio; P > 0.2 on univariate analysis; vs, versus; y, years.

[a]Estimates adjusted for all variables in the table.

[b]Among 2425 survivors without major abnormalities.

[c]Continuous variables.

[d]Dichotomous variables.

DISCUSSION

Ten, most of them small, studies evaluated ECG abnormalities in CCS who received cardiotoxic cancer treatment and survived at least two years after primary cancer diagnosis. Different ECG abnormalities occurred in CCS many years after cancer treatment, of which some can have important implications, which will be discussed further. Prevalences varied widely, likely due to clinical heterogeneity among the included studies, which made pooling of results impossible. RT involving the heart region, ≥300 mg/m^2 of anthracyclines, male gender and hypertension were identified as risk factors, at least for certain ECG abnormalities.

Some of the identified ECG abnormalities can have important implications. QTc duration was the most frequently reported ECG parameter (50% of the included studies). The major concern of prolonged QTc interval is increased risk of torsades de pointes which may have a fatal outcome[39]. Occurrence of this life threatening arrhythmia beyond the (sub)acute phase of cancer therapy is rarely reported and appears mainly triggered by additional risk factors[40-42]. Prevalence of QTc prolongation in CCS after at least two years of follow-up ranged between 0 and 15.4%; QTc dispersion prolongation was reported in 64.8%.

However, the interpretation of its clinical relevance is hampered by several factors. First, the American Heart Association and the American College of Cardiology Foundation proposed >500ms to describe a dangerously prolonged QTc interval[43]. All five studies included in this review used a more conservative definition of prolonged QT interval (i.e. >440ms). This may have led to an overestimation of CCS at risk of a serious event. Second, the variance in prevalence may be affected by differences between the study groups in for example the extent of cardiotoxic treatment [34,35]. Third, due to missing information it was not possible to evaluate other possible risk factors for QTc prolongation including female gender, age at ECG examination, follow-up time or type of cancer treatment exposure. Other factors that may have contributed are presence of genetic disorders, electrolyte abnormalities, myocardial diseases and complexity of the measurement[39,44]. Interestingly,

the prevalence of QTc prolongation decreased with increasing follow-up duration (Table 2). Prolonged QTc has been proposed as an early marker of myocardial dysfunction in CCS[45,46]. Unfortunately, none of the included studies in the present review compared QTc duration with echocardiographic measures. Overall, the available data on QTc interval is insufficient to establish its clinical relevance and should be interpreted with caution.

Other ECG abnormalities with possible clinical relevance are conduction disorders, arrhythmias, Q-waves and ST-T changes. Our results suggest that pathologic Q-waves and ST-T abnormalities occur infrequently in >2-years CCS. However, this may be an underestimation as only a few of the included studies evaluated these specific abnormalities and the attained age was relatively low. A study that was excluded for this review due to the follow-up time, evaluated 134 CCS at a mean follow-up time of 5±4 years and described a prevalence of Q-waves in 21% of CCS who were only exposed to RT involving the heart region. Interestingly, the reported ECG abnormalities were not related with shortening fraction[9]. Mulrooney et al. reported major pathologic Q-waves in 3.7% of all cancer survivors (including survivors not exposed to cardiotoxic treatment) after >10 years of follow-up and 0.7% in the control group. Only 4 of 99 CCS with Q-waves reported to have had symptoms of a myocardial infarction. On the other hand, minor pathologic Q- and QS-waves were reported more frequently (7.4%). These ECG patterns could reflect processes underlying cardiac remodeling, such as a silent previous myocardial infarction, or signify inflammation and fibrosis, all as a direct or indirect result of cardiotoxic cancer treatment[13].

Only two studies addressed the relation between possible risk factors and certain ECG abnormalities in a multivariable analysis. RT involving the heart region demonstrated the highest odds ratio of Minnesota abnormalities in one study[28]. Both studies identified male gender as a risk factor for an abnormal ECG [28,29]. Male gender as risk factor for ECG abnormalities is in line with results of the general population, hence, this risk factor may be independent of cardiotoxic treatment[14,47]. Other identified risk factors, at least for certain ECG abnormalities were ≥300 mg/m^2 of anthracyclines (including mitoxantrone), and hypertension. It is possible that no significant association between ECG abnormalities and other possible risk factors was identified because of small sample sizes/low number of events.

The key-strength of our study is the clear methodology of evidence collection. However, a couple limitations should be considered when interpreting the results. Both the number of included studies and patients are small and the included studies are very heterogeneous. In addition, methodological quality of the included studies varied, often due to a lack of reporting. Due to bias present, there may be an over- or underestimation of the prevalence

of ECG abnormalities. Also the use of exclusion criteria such as clinical heart failure and history of cardiovascular disease potentially influenced the prevalence. Moreover, it would have been interesting to evaluate whether subtle ECG abnormalities (like ST-segment changes, QTc>440 ms, PVCs, and minor Q-wave abnormalities) occurred more frequently in CCS than in the general population. Unfortunately, only the study of Mulrooney et al. included community controls[28]. Overall, only 10% of the included studies scored 'good' on external validity indicators and 10% 'bad' on all applicable items. In 90% of studies, important information with regard to treatment was missing and in 20% of studies the length of follow-up was not reported. As there might be a latency period for the development of ECG abnormalities, the length of follow-up in some studies could have been too short for participants to develop ECG abnormalities. In 50% of the studies, the outcome was not well-defined, so either the method of detection, the definition of an abnormal outcome used in the study or both were not provided. In both studies that conducted multivariable analyses of potential risk factors these analyses were well-defined.

We need to better understand whether ECG could improve the cardiac care of CCS. Although the role of ECG seems limited in early detection of systolic dysfunction[10,13], ECG markers such as QTc time and Minnesota Criteria may aid in the risk stratification since these are associated with development of left ventricular systolic dysfunction and future cardiac events[18,20-22,28,48,49]. In addition, evaluation of pathologic Q-waves or ST-T abnormalities may reflect cardiac remodeling which may remain subclinical and may not be apparent on echocardiography as myocardial dysfunction. Clinicians should be aware of these ECG patterns as severe cardiac ischemia can already occur at age <30 years[50].

The debate whether ECG examination should be incorporated in the surveillance of long-term CCS is mainly driven by the uncertainty of its added value. Drawing conclusions from the current systematic review is challenging, but nevertheless, it is critical to emphasize the importance of more investigation in this field. Large prospective studies, clear definitions of ECG abnormalities and comparison with a control group are warranted.

CONCLUSION

Various ECG abnormalities have been described in CCS years after cardiotoxic treatment, some of which can have important implications. Risk factors include male sex, anthracyclines ≥300 mg/m^2, RT involving the heart region and hypertension. Large studies are needed to evaluate the exact long-term incidence of ECG abnormalities following cardiotoxic treatment and associated risk factors, and to investigate their clinical relevance and relation with cardiac dysfunction or future cardiac events.

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SUPPLEMENTAL MATERIAL

Table 1. Search strategies

Table 2. The preference order to choose the best report in case of overlapping cohorts

Table 3. Risk of bias assessment criteria for observational studies

Table 4. Detection methods, used definitions and detailed prevalence of electrocardiographic abnormalities

Supplemental Table 4 (Support for judgement of risk of bias) is not included in this thesis. It can be found online in: Pediatr Blood Cancer. 2022 Aug;69(8):e29720. doi: 10.1002/pbc.29720. Epub 2022 Apr 28.

Table 1. Search strategies

Medline
#1 "Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR "Pediatrics"[Mesh] OR "Minors"[Mesh] OR "Young Adult"[Mesh] OR child*[tiab] OR infan*[tiab] OR baby[tiab] OR babies[tiab] OR newborn*[tiab] OR new-born*[tiab] OR neonat*[tiab] OR perinat*[tiab] OR toddler*[tiab] OR adolescen*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR teen*[tiab] OR youth*[tiab] OR young age[tiab] OR minors*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR juvenil*[tiab] OR boy*[tiab] OR girl*[tiab] OR schoolchild*[tiab] OR school child*[tiab] OR kid[tiab] OR kids[tiab] OR young male*[tiab] OR young female*[tiab] OR young adult*[tiab] OR young man[tiab] OR young men[tiab] OR young woman[tiab] OR young women[tiab]
#2 "Anthracyclines"[Mesh] OR anthracyclin*[tiab] OR antracyclin*[tiab] OR doxorubic*[tiab] OR dox sl[tiab] OR daunorubic*[tiab] OR NSC 82151[tiab] OR NSC-82151[tiab] OR demethoxydaunorubic*[tiab] OR IMI 30[tiab] OR IMI-30[tiab]OR IMI30[tiab] OR NSC 256439[tiab] OR NSC-256439[tiab] OR idarubic*[tiab] OR epidoxorubic*[tiab] OR epi dxr[tiab] OR NSC 256942[tiab] OR NSC-256942[tiab] OR IMI 28[tiab] OR IMI-28[tiab] OR IMI28[tiab] OR epirubic*[tiab] OR adriamyc*[tiab] OR epiadriamyc*[tiab] OR plicamyc*[tiab] OR farmorubic*[tiab] OR rubidomyc*[tiab] OR rubomyc*[tiab] OR daunomyc*[tiab] OR adriablastin*[tiab] OR adriblastin*[tiab] OR cerubidin*[tiab] OR daunoblastin*[tiab] OR daunoxom*[tiab] OR daunosom*[tiab] OR doxil[tiab] OR caelyx[tiab] OR myocet[tiab] OR "Antineoplastic Agents"[Mesh] OR "Neoplasms/drug therapy"[Mesh] OR "Neoplasms/radiotherapy"[Mesh] OR "Radiotherapy"[Mesh] OR radiotherap*[tiab] OR radiation therap*[tiab] OR "radiotherapy" [Subheading] OR chemoradiother*[tiab] OR radiochemo*[tiab] OR "Mitoxantrone"[Mesh] OR mitoxantrone*[tiab] OR Mitozantrone[tiab] OR DHAQ[tiab] OR NSC-279836[tiab] OR NSC 279836[tiab] OR NSC279836[tiab] OR NSC-287836[tiab] OR NSC 287836[tiab] OR NSC287836[tiab] OR NSC-299195[tiab] OR NSC 299195[tiab] OR NSC299195[tiab] OR NSC-301739[tiab] OR NSC 301739[tiab] OR NSC301739[tiab] OR NSC-301739D[tiab] OR NSC 301739D[tiab] OR NSC301739D[tiab] OR Mitroxone[tiab] OR Pralifan[tiab] OR CL-232325[tiab] OR CL 232325[tiab] OR CL232325[tiab] OR Ralenova[tiab] OR Novantron*[tiab] OR Onkotrone[tiab]
#3 "Electrocardiography"[Mesh] OR electrocardio*[tiab] OR ecg[tiab] OR ekg[tiab]
Final search = #1 AND #2 AND #3
Embase
#1 Infan$:ti,ab,kw OR new?born$:ti,ab,kw OR newborn$:ti,ab,kw OR childhood/exp OR baby$:ti,ab,kw OR babies:ti,ab,kw OR toddler$:ti,ab,kw OR minors$:ti,ab,kw OR boy:ti,ab,kw OR boys:ti,ab,kw OR boyhood:ti,ab,kw OR girl$:ti,ab,kw OR kid:ti,ab,kw OR kids:ti,ab,kw OR child/exp OR child$:ti,ab,kw OR children:ti,ab,kw OR school child:ti,ab,kw OR school$:ti,ab,kw OR schoolchild$:ti,ab,kw OR school child$:ti,ab,kw OR adolescen$:ti,ab,kw OR youth$:ti,ab,kw OR young age:ti,ab,kw OR teen$:ti,ab,kw OR juvenile$:ti,ab,kw OR underage:ti,ab,kw OR pubescen$:ti,ab,kw OR p?ediatric$/exp OR premature$:ti,ab,kw OR preterm$:ti,ab,kw OR young adult/exp OR young adult$:ti,ab,kw OR young woman:ti,ab,kw OR young women:ti,ab,kw OR young man:ti,ab,kw OR young men:ti,ab,kw OR young male:ti,ab,kw OR young female:ti,ab,kw OR childhood cancer survivor/exp

#2 'antineoplastic antibiotic'/exp OR 'antineoplastic antibiotic':ti,ab,kw OR 'cancer chemotherapy'/exp OR 'cancer chemotherapy' OR 'cancer chemotherapy':ti,ab,kw OR anthracyclin*:ti,ab,kw OR antracyclin*:ti,ab,kw OR 'anthracycline antibiotic agent'/exp OR daunoxom*:ti,ab,kw OR daunosom*:ti,ab,kw OR doxil:ti,ab,kw OR caelyx:ti,ab,kw OR myocet:ti,ab,kw OR doxorubic*:ti,ab,kw OR nsc?82151:ti,ab,kw OR nsc82151:ti,ab,kw OR cerubidin*:ti,ab,kw OR daunoblastin*:ti,ab,kw OR daunorubic*:ti,ab,kw OR adramyc*:ti,ab,kw OR adriamyc*:ti,ab,kw OR adriablastin*:ti,ab,kw OR adriblastin*:ti,ab,kw OR dox?sl:ti,ab,kw OR imi?28:ti,ab,kw OR imi28:ti,ab,kw OR nsc256942:ti,ab,kw OR nsc?256942:ti,ab,kw OR epirubic*:ti,ab,kw OR farmorubic*:ti,ab,kw OR nsc?256439:ti,ab,kw OR nsc256349:ti,ab,kw OR imi30:ti,ab,kw OR imi?30:ti,ab,kw OR idarubic*:ti,ab,kw OR 4?demethoxydaunorubi*:ti,ab,kw OR demethoxydaunorubic*:ti,ab,kw OR 4?desmethoxydaunorubi*:ti,ab,kw OR 'desmeth oxydaunorubic*':ti,ab,kw OR 4?epi?adriamy*:ti,ab,kw OR epiadriamyc*:ti,ab,kw OR '4 epiadriamy*':ti,ab,kw OR 4?epi?dxr:ti,ab,kw OR dxr:ti,ab,kw OR 'radiotherapy'/exp OR 'radiotherap*':ti,ab,kw OR 'radiation therap*':ti,ab,kw OR chemoradiotherap*:ti,ab,kw OR radiochemotherap*:ti,ab,kw OR 'mitoxantrone'/exp OR mitoxantrone:ti,ab,kw OR mitozantrone:ti,ab,kw OR dhaq:ti,ab,kw OR nsc?279836:ti,ab,kw OR nsc?287836:ti,ab,kw OR nsc?299195:ti,ab,kw OR nsc?301739:ti,ab,kw OR nsc?301739d:ti,ab,kw OR mitroxone:ti,ab,kw OR pralifan:ti,ab,kw OR cl?232325:ti,ab,kw OR novantrone:ti,ab,kw OR ralenova:ti,ab,kw OR novantron*:ti,ab,kw OR onkotrone:ti,ab,kw

#3 electrocardiography/exp OR electrocardiograph/exp OR electrocardiogram/exp OR electrocardio*:ti,ab,kw OR ecg:ti,ab,kw OR ekg:ti,ab,kw

#4 [article]/lim OR [article in press]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim) AND [embase]/lim

Final search = #1 AND #2 AND #3 AND #4

CENTRAL

#1 (child*)ti,ab,kw OR (infant*)ti,ab,kw OR (baby)ti,ab,kw OR (babies)ti,ab,kw OR (newborn*) ti,ab,kw OR (new-born*)ti,ab,kw OR (neonat*)ti,ab,kw OR (perinat*)ti,ab,kw OR (toddler*)ti,ab,kw OR (adolescen*)ti,ab,kw OR (pubescen*)ti,ab,kw OR (teen*)ti,ab,kw OR (youth*)ti,ab,kw OR (young age)ti,ab,kw OR (minors*)ti,ab,kw OR (pediatric*)ti,ab,kw OR (paediatric*)ti,ab,kw OR (juvenil*) ti,ab,kw OR (boy)ti,ab,kw OR (boyhood)ti,ab,kw OR (girl*)ti,ab,kw OR (schoolchild*)ti,ab,kw OR (school child*)ti,ab,kw OR (kid)ti,ab,kw OR (kids)ti,ab,kw OR (young male)ti,ab,kw OR (young female)ti,ab,kw OR (young adult*)ti,ab,kw OR (young men)ti,ab,kw OR (young woman)ti,ab,kw OR (young man)ti,ab,kw OR (young women)ti,ab,kw)

#2 ((anthracyclin*)ti,ab,kw OR (antracyclin*)ti,ab,kw OR (doxorubic*)ti,ab,kw OR (dox sl)ti,ab,kw OR (daunorubic*)ti,ab,kw OR (NSC 82151)ti,ab,kw OR (demethoxydaunorubic*)ti,ab,kw OR (IMI 30)ti,ab,kw (IMI30)ti,ab,kw OR (NSC 256439)ti,ab,kw OR (idarubic*)ti,ab,kw OR (epidoxorubic*) ti,ab,kw OR (epi dxr)ti,ab,kw OR (NSC 256942)ti,ab,kw OR (IMI 28)ti,ab,kw OR (IMI28)ti,ab,kw OR (epirubic*)ti,ab,kw OR (adriamyc*)ti,ab,kw OR (epiadriamyc*)ti,ab,kw OR (plicamyc*)ti,ab,kw OR (farmorubic*)ti,ab,kw OR (rubidomyc*)ti,ab,kw OR (rubomyc*)ti,ab,kw OR (daunomyc*)ti,ab,kw OR (adriablastin*)ti,ab,kw OR (adriblastin*)ti,ab,kw OR (cerubidin*)ti,ab,kw OR (daunoblastin*) ti,ab,kw OR (daunoxom*)ti,ab,kw OR (daunosom*)ti,ab,kw OR (doxil)ti,ab,kw OR (caelyx) ti,ab,kw OR (myocet)ti,ab,kw OR (Radiotherap*)ti,ab,kw OR (Radiation Therap*)ti,ab,kw OR (chemoradiotherap*)ti,ab,kw OR (radiochemotherap*)ti,ab,kw OR (mitoxantrone)ti,ab,kw OR (mitozantrone)ti,ab,kw OR (dhaq)ti,ab,kw OR (nsc 279836)ti,ab,kw OR (nsc279836)ti,ab,kw OR (nsc 287836)ti,ab,kw OR (nsc287836)ti,ab,kw OR (nsc 299195)ti,ab,kw OR (nsc299195)ti,ab,kw OR (nsc 301739)ti,ab,kw OR (nsc301739)ti,ab,kw OR (nsc 301739d)ti,ab,kw OR (nsc301739d)ti,ab,kw OR (mitroxone)ti,ab,kw OR (pralifan)ti,ab,kw OR (cl 232325)ti,ab,kw OR (cl232325)ti,ab,kw OR (novantrone)ti,ab,kw OR (ralenova)ti,ab,kw OR (novantron*)ti,ab,kw OR (onkotrone)ti,ab,kw)

#3 ((electrocardio*)ti,ab,kw OR (ecg)ti,ab,kw OR (ekg)ti,ab,kw)

Final search = #1 AND #2 AND #3

Table 2. The preference order to choose the best report in case of overlapping cohorts

1	original report combining findings of two or more reports
2	the latest report containing more subjects
3	the original paper, unless subsample analysis has more useful data.

Table 3: Risk of bias assessment criteria for observational studies

	Internal validity	***External validity***
Study group	**Selection bias (representative: yes/no)** • if the described study group consisted of more than 90% of the original cohort of childhood cancer survivors treated with cardiotoxic treatment • or if it was a random sample with respect to the cancer treatment and important prognostic factors (i.e. age, gender, co-treatment)	**Reporting bias (well-defined: yes/no):** • if the mean/median or range of the cumulative doses of cardiotoxic therapy were mentioned
Follow-up	**Attrition bias (adequate: yes/no)** • if the outcome was assessed for more than 90% of the study group of interest (++) • or if the outcome was assessed for 60-90% of the study group of interest (+)	**Reporting bias (well defined: yes/no)** • if the length of follow-up was mentioned
Outcome	**Detection bias (blind: yes/no)** • if the outcome assessors were blinded to the investigated determinant	**Reporting bias (well-defined: yes/no):** • if the method of detection and the definition of an abnormal ECG pattern were provided
Risk assessment	**Confounding (adjustment for other factors: yes/no)** • if important prognostic factors (i.e. age, gender, co-treatment) or follow-up were taken adequately into account	**Analyses (well defined: yes/no)** • if a relative risk, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated

Table 5. Detection methods, used definitions and detailed prevalence of electrocardiographic abnormalities

1st author, year.	Method & definition ECG abnormality	Prevalence (n/N with ECG examination (%))			
Caru, 2019.	Three-channel 24-h Holter monitor. Vetricular arrhythmias: the Myerburg classification(1).		Standard risk*	High risk *	Total
		Ventricular arrhythmias			
		Class 0 (no VPCs)	0/89 (0)	2/51 (3.9)	2/140 (1.4)
		Class I (<1 VPC/h)	24/89 (27)	20/51 (39.2)	44/140 (31.4)
		Class II (1-9 VPCs/h)	53/89 (59.6)	24/51 (47.1)	77/140 (55)
		Class III (10-29 VPCs/h)	7/89 (7.8)	5/51 (9.8)	12/140 (8.6)
		Class IV (≥30 VPCs/h)	5/89 (5.6)	0/51 (0)	5/140 (3.6)
Materazzo, 2017.	12 lead ECG. Significant ECG abnormalities duringor after stress echocardiogram. definitions nm.	0/53 (0)			
Mulrooney, 2017.	12 lead ECG in rest. Major and minor ECG abnormalities classified by the Minnesota Code (MC) (2).	Major abnormalities Minor abnormalities	Anthracycline only: nm/nm (8.5) Cardiac RT only: nm/nm (18.3) Anthracyclines and cardiac RT: nm/nm (17.3) Alkylators and anthracyclines: nm/nm (7.1) Alkylators and cardiac RT: nm/nm (23.2) Alkylators, anthracyclines and cardiact RT: nm/nm (17.3) nm		
Pourier, 2017.	12 lead ECG. Abnormal ECG pattern: based on the MC (REF2), prolonged QTc interval= >450 msec, aspecific repolarization abnormality (defintion nm), aspecific IVCA: (definition nm) *Major ECG abnormalities*	Abnormal ECG pattern	73/340 (21.5)		
		QRS axis deviation (MC 2)	1/340 (0.3)		
		High-amplitude R waves (MC 3)	*14/340 (4.1)*		
		T-wave items (MC 5)	1/340 (0.3)		
		AV conduction defect: (MC 6)	4/340 (1.2)		
		Ventricular conduction disorders (MC 7)	29/340 (8.5)		
		- LBBB (MC 7-1-1)	*1/340 (0.3)*		
		- RBBB (MC 7-1-2)	*1/340 (0.3)*		
		- IRBBB (MC 7-3)	24/340 (7.1)		
		- LAH (MC 7-7)	3/340 (0.9)		
		Sinus bradycardia (MC 8)	9/340 (2.6)		
		Prolonged QTc	2/340 (0.6)		
		Aspecific repolarization abnormality	3/340 (0.9)		
		Aspecific IVCA	4/340 (0.9)		

1st author, year.	Method & definition ECG abnormality	Prevalence (n/N with ECG examination (%))			
Pourier, 2015.	ECG. Signs of myocardial infarction: ST- elevation, ST-depression, pathological Qs. Exact definitions nm.	0/57 (0)			
Landier, 2012.	ECG. Prolonged QTc interval= > 450 msec msec males; > 470 females,	7/248 (2.8)			
Rajic, 2009.	12 lead ECG. Abnormal = clear conduction disturbances, depolarization, and repolarization changes; definitions nm.	22/76 (29)			
Gupta, 2002.	12 lead ECG. Prolonged QTc interval = >450 msec. Prolonged QTcd = > 65 msec		Shortening fraction ≥29%	Shortening fraction <29%	Total
		Prolonged QTc	2/39 (5)	2/15 (15)	4/54 (7)
		Prolonged QTcd	27/39 (66)	8/15 (62)	35/54 (65)
Rammeloo, 2000.	12 lead ECG. Prolong QTc = QTc >440 msec. Decreased QRS voltage, T-wave inversion, ST-T abnormalities, and supraventricular and ventricular arrhythmias. Exact definitions nm.	12 lead ECG Prolonged QTc Microvoltage in leads I, II, III Flattened T waves ST-T abnormalities Supraventricular arrhythmias Ventricular arrhythmias	 0/50 (0) 1/50 (2) 1/50 (2) 0/50 (0) 0/50 (0) 0/50 (0)		
Schwartz, 1993.	ECG in rest. Prolonged QTc = ≥ 450 msec	8/52 (15)			

* Risk classification based on gender, age, time from end treatment and prognostic risk group.

AV= atrioventricular, ECG= elektrocardiography, IVCA = intraventricular conduction abnormalities, IRBBB= incomplete right bundle branch block, msec = milisecond, mV= miliVolt, MC = Minnesota Code, LAH= left anterior hemiblock, LBBB=left bundle branch block, PAC= premature atrial complex, PVC=premature ventricular complex, RBBB= right bundle branch block, 24-h= 24 hour,

References

1. Myerburg RJ, Kessler KM, Luceri RM, Zaman L, Trohman RG, Estes D, et al. Classification of ventricular arrhythmias based on parallel hierarchies of frequency and form. The American journal of cardiology. 1984;54(10):1355-8.
2. Prineas RJ, Crow RS, Zhang Z. The Minnesota Code Manual of Electrocardiographic Findings2009.

4.2

ELECTROCARDIOGRAPHIC ABNORMALITIES IN CHILDHOOD CANCER SURVIVORS: A DCCSS LATER 2 CARD STUDY

Esmée C. de Baat, Remy Merkx, Jan M. Leerink, Coen Boerhout, Helena J.H. van der Pal, Elvira C. van Dalen, Jacqueline Loonen, Dorine Bresters, Eline van Dulmen-den Broeder, Margriet van der Heiden-van der Loo, Marry M. van den Heuvel-Eibrink, Judith L. Kok, Marloes Louwerens, Sebastian J.C.M.M. Neggers, Cécile M. Ronckers, Jop C. Teepen, Wim J.E. Tissing, Andrica C. de Vries, Livia Kapusta, Leontien C.M. Kremer, Annelies .M.C. Mavinkurve-Groothuis, Wouter E.M. Kok*, Elizabeth A.M. Feijen*

*shared last-authors

Submitted

ABSTRACT

Background - Cardiomyopathy surveillance guidelines for childhood cancer survivors recommend a single electrocardiographic (ECG) examination, but its precise role remains unclear.

Objective - We assessed the prevalence of ECG abnormalities, their association with left ventricular (LV) dysfunction, and their diagnostic value in cardiomyopathy surveillance among childhood cancer survivors.

Methods - This Dutch Childhood Cancer Survivor Study included ≥5-year survivors and their siblings. We identified ECG abnormalities, based on the Minnesota Code, associated them with LV dysfunction by LASSO and evaluated their added value using logistic regression models. Calibration was tested with the Hosmer-Lemeshow test and bootstrap analysis was used for internal validation.

Results - We included 1,381 survivors exposed to (potentially) cardiotoxic cancer treatment (48% male, median age 35 years, median follow-up 27 years) and 272 siblings (40% male, median age 37 years). Major ECG abnormalities occurred in 16% of survivors compared to 14% of siblings and minor ECG abnormalities in 57% of survivors and in 50% of siblings. Left bundle branch block, left atrial enlargement, left heart axis, Cornell's criteria for LV hypertrophy and heart rate were independently associated with LVEF<45% and significantly improved the discriminatory ability of the baseline regression model (c-statistic 0.80 versus 0.86). To assume absence of LVEF<45% with an estimated probability of <1%, sensitivity of the model including ECG was 93%, specificity was 56% and negative predictive value was 99.6%. Calibration and internal validation tests performed well.

Conclusion - Specific ECG abnormalities are clearly associated with reduced LVEF in survivors at risk of cardiomyopathy and may have an added value in surveillance to rule-out LVEF<45%.

BACKGROUND

Over the past decades survival rates of children with cancer have improved considerably[1]. Unfortunately, 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 to the general population[2-4]. The cardiotoxic effects of cancer treatment may present as myocardial dysfunction, cardiac ischemia, pericarditis, valvular disease or arrhythmias[5-8].

Cardiomyopathy surveillance with echocardiography is an important part of cardiac care for survivors who are at risk[9]. 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 to perform electrocardiographic (ECG) examination 5 years after cancer diagnosis as a baseline recording and thereafter on indication[9,10]. However, the precise role and added value of ECG abnormalities in the surveillance of cardiomyopathy remain unclear[11,12].

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[13]. The Minnesota Code, a standardized coding system to support universal interpretation of ECG abnormalities in population studies[14], provides a systematic and transparent method to define ECG abnormalities[14]. In large cohort studies from the general population, it was demonstrated that certain ECG abnormalities, described according to the Minnesota Code, predict future cardiac events including heart failure[15-17]. In survivors, the presence of major ECG abnormalities has been shown to be predictive of overall mortality[18].

Besides predicting future events, ECG variables demonstrated a sensitivity up to 98% with varying specificity in the diagnosis of left ventricular (LV) systolic dysfunction in different populations[19-21]. The sensitivity and negative predictive value may however be influenced by different definitions of LV dysfunction, different definitions of ECG abnormalities and the prior probability of LV dysfunction[22,23]. Because of a high sensitivity, but low specificity, the European Society of Cardiology guideline recommends routine use of an ECG primarily to rule out heart failure[23]. The diagnostic performance of conventional ECG abnormalities for LV dysfunction has not been evaluated yet and needs to be assessed in relation to other variables predicting cardiotoxicity.

In this cross-sectional cardiac sub-study of the Dutch Childhood Cancer Survivor study we assessed the prevalence of ECG abnormalities, based on the Minnesota Code, in survivors who were treated with (potentially) cardiotoxic cancer treatment and their siblings. We aimed to identify a composite of ECG abnormalities that is associated with LV systolic dysfunction and to evaluate the potential added diagnostic value of ECG abnormalities in cardiomyopathy surveillance in a large cohort of survivors.

METHODS

Study population

This cardiac sub-study is part of the cross-sectional Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort (1963-2001) part 2; clinical visit & questionnaire study and focusses on early detection of subclinical cardiac dysfunction by different surveillance modalities. Details of the methods have been published before[24]. In short, the study comprised ≥5-year survivors from multiple Dutch centers 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), and sibling controls. All survivors who were diagnosed with childhood cancer at age <18 years between 1/1/1963 and 12/31/2001, 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. Participants visited the outpatient clinic between February 2016 and February 2020 for questionnaires, physical examination, blood sampling, ECG and echocardiography. The DCCSS LATER 2 conforms to the principles outlined in the Declaration of Helsinki and was approved by the medical ethics board of all participating centers. Informed consent was obtained from all participants.

Data collection

We extracted patient and cancer treatment characteristics from the central database of DCCSS LATER. For alkylating agents and anthracyclines, we used an equivalent ratio to calculate the dose[25-27]. Mitoxantrone, an anthraquinone with large cardiotoxic potential[25], was not included in the anthracycline dose. We estimated radiotherapy dose received by the heart with a standardized protocol (see Supplementary file A). Participants provided information about their medical history, cardiovascular risk factors and medication use through questionnaires and during visits to outpatient clinics. Chronic cardiovascular

medication use was coded according to the Anatomical Therapeutic Chemical classification[28]. Self-reported history of heart failure, myocardial infarction, arrhythmia, arterial hypertension and diabetes were validated against use of appropriate medication.

All participants underwent physical examination, 12-lead resting ECG examination and echocardiography. Multiple trained observers were blinded for the clinical characteristics and analyzed the ECGs under a standardized protocol including quality assessment[29]. In case of unacceptable quality we excluded the specific lead(s) for further analysis. We used the Minnesota Code to define ECG abnormalities[14]. 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 the minor Minnesota Codes 7-10 and 9-7, because new criteria for early repolarization and fragmented QRS have been proposed[30-32]. In addition, we evaluated heart rate, QRS-duration and QTc duration as continuous variables and Cornell's criteria for left ventricular 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[17,33,34]. Systolic left ventricular function was assessed by biplane left ventricular ejection fraction (LVEF) on echocardiography. Its protocol, reproducibility and feasibility were previously published[35]. To evaluate at which level of systolic dysfunction ECG abnormalities start to occur, we studied a LVEF cut-off <52% in males/54% in females[36] and for more severe LV dysfunction a cut-off <45%. The number of survivors with LVEF<40% was too low to allow meaningful analysis.

Statistical analysis

The prevalence of survivors with ECG abnormalities was calculated in all survivors and in each of the (potentially) cardiotoxic cancer treatment groups. The results were compared to those of siblings with the Chi-square test or Fisher 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.

To identify ECG abnormalities associated with systolic dysfunction, we included survivors who received anthracyclines, mitoxantrone and/or heart RT, without a previous diagnosis of cardiomyopathy to reflect the surveillance population. We assessed the association between ECG variables and the occurrence of systolic dysfunction with multivariable logistic regression models. We started with a baseline model including sex, age at diagnosis, age at ECG examination and treatment with anthracyclines, mitoxantrone and heart RT as these are well-established risk factors of cardiotoxicity[37,38]. To identify ECG

abnormalities that are associated with systolic dysfunction we used the LASSO method to select which of the predefined ECG abnormalities and continuous ECG measures were best discriminating between an abnormal and normal systolic function and added them to the baseline model, including the well-established risk factors of cardiotoxicity. For ease of use and model performance, we created a variable "abnormal ECG based on LASSO analysis" based on the ECG abnormalities that remained significantly associated with abnormal systolic function and we manually excluded noncontributing continuous ECG measures in this new variable.

To evaluate the potential added diagnostic value of ECG in cardiomyopathy surveillance we quantified the discriminative ability of the models with and without ECG abnormalities by the c-statistic and tested the calibration with the Hosmer-Lemeshow statistics (dividing the data into 10 groups)[39]. We internally validated the final model with a bootstrap analysis (1000 resamples). We used an estimated probability of <1% and <5% to assume absence of systolic dysfunction and calculated the according diagnostic accuracy.

SPSS (version 26) and R version (4.0.3) were used for statistical analysis, and p-value <0.05 was considered statistically significant.

Table 1. Characteristics of the analyzed survivors and siblings

Variables	Survivors					Siblings
	All survivors n=1,381[a]	Only anthracyclines/ mitoxantrone n=809	Only heart RT n=158	Heart RT and anthracyclines/ mitoxantrone n=253	Potentially cardiotoxic therapy n=155	n=272
Sex, No. (%)						
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, No. (%)	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, No. (%)						
Leukemias	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 tumors	43 (3)	19 (2)	16 (10)	8 (3)	1 (1)	
Retinoblastoma	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (1)	
Renal tumors	165 (12)	41 (5)	44 (28)	61 (24)	19 (12)	
Hepatic tumors	11 (1)	11 (1)	0 (0)	0 (0)	0 (0)	
Bone tumors	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 tumors	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, No. (%)	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)

Variables	Survivors					Siblings
	All survivors n=1,381[a]	Only anthracyclines/ mitoxantrone n=809	Only heart RT n=158	Heart RT and anthracyclines/ mitoxantrone n=253	Potentially cardiotoxic therapy n=155	n=272
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, No. (%)	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[b], mg/m²						
Median (IQR)	180 [120-288]	180 [120-288]		200 [150-299]		
No anthracyclines, No. (%)	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/m²						
Median (IQR)	40 [20-72]	44 [20-93]		20 [20-50]		
No mitoxantrone, No. (%)	1308 (95)	755 (94)	158 (100)	234 (93)	155 (100)	
1-40	40 (3)	26 (3)		14 (6)		
>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, No. (%)	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, No. (%)	1,153 (70)	690 (85)	237 (94)	102 (65)	118 (76)	
Ifosfamide exposed, No. (%)	207 (15)	109 (14)	5 (3)	77 (30)	14 (9)	
Cyclophosphamide exposed, No. (%)	774 (57)	552 (68)	39 (30)	157 (62)	23 (15)	

Variables	Survivors					Siblings
	All survivors n=1,381[a]	Only anthracyclines/ mitoxantrone n=809	Only heart RT n=158	Heart RT and anthracyclines/ mitoxantrone n=253	Potentially cardiotoxic therapy n=155	n=272
Outpatient clinic data						
Waist circumference, cm	86 [78-94]	85 [78-94]	88 [80-97]	83 [75-90]	88 [81-96]	86 [80-95]
Systolic blood pressure, mmHg	121 [112-132]	120 [112-129]	130 [118-142]	119 [110-131]	122 [112-134]	119 [109-128]
Diastolic blood pressure, mmHg	75 [68-81]	74 [68-81]	78 [72-84]	75 [68-81]	75 [67-82]	73 [66-79]
Impaired LVEF at evaluation[c], No. (%)	294 (21)	160 (22)	31 (23)	84 (38)	16 (14)	13 (5)
Severe impaired LVEF at evaluation[d], No. (%)	57 (5)	36 (5)	4 (3)	17 (8)	0 (0)	0 (0)
Questionnaire data, No. (%)						
Ever smoked >1 year[e]	377 (27)	231 (31)	43 (28)	67 (29)	35 (24)	79 (37)
Self-reported diagnosis of hypertension[f]	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)
Self-reported diagnosis of diabetes[f]	26 (3)	8 (1)	9 (6)	7 (3)	2 (1)	0 (0)
Self-reported diagnosis of arrhythmia[f]	16 (1)	7 (1)	6 (4)	3 (1)	0 (0)	0 (0)
Self-reported diagnosis of MI[f]	4 (0.3)	1 (0.1)	1 (1)	2 (1)	0 (0)	0 (0)
Self-reported diagnosis of heart failure[f]	48 (4)	27 (4)	4 (3)	17 (7)	0 (0)	0 (0)
Self-reported history of cardiac surgery	23 (2)	8 (1)	8 (5)	5 (2)	2 (1)	0 (0)
Self-reported history of CHD	26 (2)	18 (2)	2 (1)	2 (1)	4 (3)	2 (1)

[a] In 6 survivors the cardiotoxic cancer treatment was unclear due to missing information on either anthracycline exposure or heart RT.

[b] Calculated as doxorubicin + daunorubicin*0.5 + epirubicine*0.8 + idarubicine*3.

[c] Defined as LVEF below normal threshold < 54% (females) or <52% (males). Missing in 198.

[d] Defined as LVEF <45%. Missing in 198.

[e] Composite of DCCSS LATER study part 1 and 2. Missing in 164.

[f] Missing in 111 for hypertension, in 106 for diabetes, in 114 for arrhythmia, in 106 for myocardial infraction.

CHD = congenital heart disease, IQR=interquartile range, LVEF= left ventricular ejection fraction, MI = myocardial infraction, n=number, RT = radiotherapy, y=year.

RESULTS

Study population

Figure 1 shows the inclusion flowchart of the survivors in this study which eventually comprised 1,381 survivors (52% female). Leukemia (41%), lymphoma (24%) and renal tumors (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 to 13 (5%) siblings. There were 57 (5%) survivors with LVEF<45%. We excluded 29 of these 57 survivors for the diagnostic value analysis because of a previous (n=23) or unknown (n=6) cardiomyopathy diagnosis/pacemaker (n=23). Supplementary 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 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). As demonstrated in Figure 2, differences in prevalence became more apparent after we divided the survivors into different cardiotoxic cancer treatment exposure groups. 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% which was significantly higher when compared to siblings, also when adjusted for age at ECG and sex. This latter group of survivors received the highest heart RT doses (Table 1).

Minor ECG abnormalities were detected in 57% of the survivors versus 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%). Supplementary file C shows the prevalence of the separate major, minor and other ECG abnormalities in survivors and siblings. The prevalence of the individual ECG abnormalities increased with decreasing LVEF and only became significantly different from the survivors with normal systolic function when the LVEF was <45% (Supplementary file D).

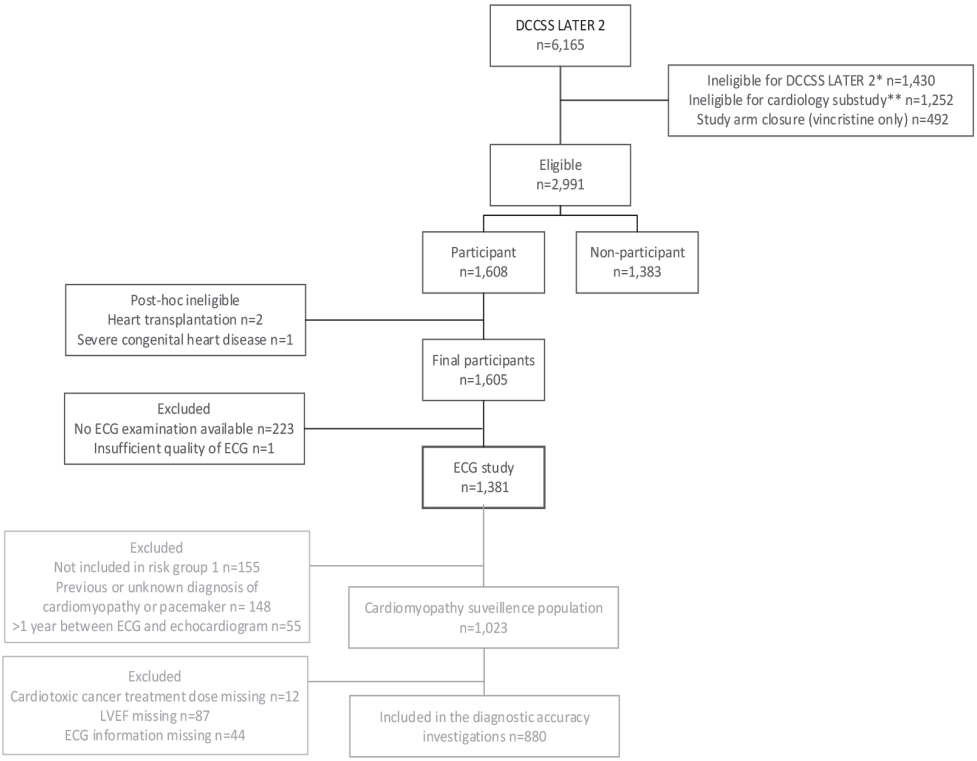


Figure 1. Flowchart of the study

* 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 = the Dutch Childhood Cancer Survivor Study, LATER cohort (1963-2001) part 2; ECG= electrocardiogram; n= number.

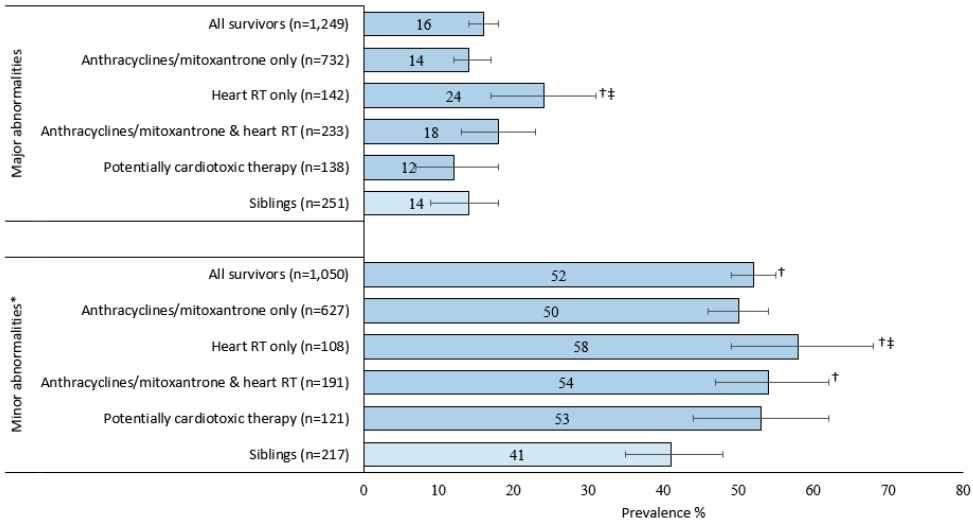


Figure 2. Comparison of the prevalence of any major and minor ECG abnormality between survivors (all and per cardiotoxic cancer exposure) and siblings, both adjusted and unadjusted for sex and attained age

†unadjusted comparison with siblings demonstrated a p-value <0.05.

‡ comparison with siblings, adjusted for sex and age at ECG, demonstrated a p-value <0.05

The added diagnostic value of ECG in cardiomyopathy surveillance

To identify a composite of specific ECG abnormalities associated with systolic dysfunction we performed the multivariable analyses with LVEF<45% as outcome (Table 2) and the models with LVEF<52/54% as outcome (Supplementary file D). These models included 880 of the 1,226 survivors who were exposed to cardiotoxic cancer treatment, with the exclusion of those who had a previous or unknown diagnosis of cardiomyopathy or a pacemaker. In addition, a small group of survivors were excluded from this analysis due to missing cardiotoxic cancer treatment dose, missing LVEF or missing ECG information (see Figure 1).

The baseline model for a LVEF<45% including patient and treatment-related risk factors and no ECG values yielded a c-statistic of 0.80 (95% CI 0.72-0.87). The LASSO method selected five ECG abnormalities and two continuous measures that discriminated best between LVEF≥45% and <45%. 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%. Hence, if one or more of these abnormalities were present the variable "abnormal ECG based on LASSO analysis" was classified as 'yes'. 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 (Supplement File D).

We evaluated the added diagnostic value for the models presented in Table 2 and supplementary file D. The addition of "abnormal ECG based on LASSO analysis" and heart rate to the baseline model contributed significantly to the diagnosis of LVEF<45% as the AIC decreased with 25 points (c-statistic 0.86, 95% CI 0.78-0.93). The odds ratio (OR) of "abnormal ECG based on LASSO analysis" was 7.2 (95% CI 3.0-18.0), and the OR for increased heart rate (in steps of 10) was 1.5 (95% CI 1.1-2.1). 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. As demonstrated in Supplementary file D, the association between ECG data and LVEF<52/54% was less strong and the final model demonstrated a c-statistic of 0.71 compared to a c-statistic of 0.66 when using the model without ECG data.

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

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

[a] We could not analyse n=143 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.

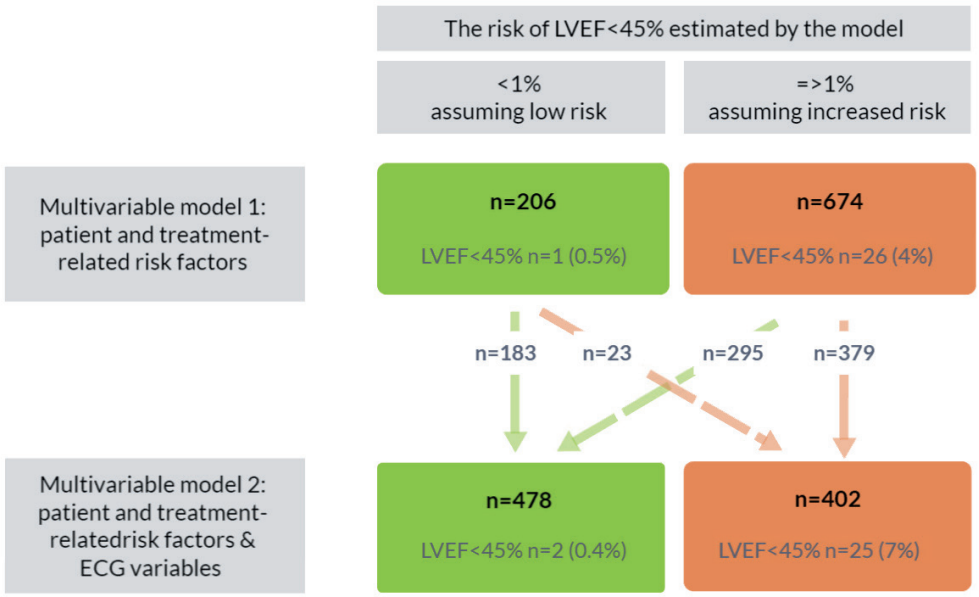
AIC= Akaike information criterion, CI=confidence interval, ECG=electrocardiography, LVEF = left ventricular ejection fraction, OR = odds ratio

Table 3. The diagnostic accuracy of the model including ECG at different probability thresholds to assume a low risk of LVEF<45% in the cardiomyopathy surveillance group

Estimated probability to assume low risk of LVEF<45%	LVEF <45% n (%)	LVEF ≥45% n (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<1%	2 (0.4)	476 (99.6)	93 (76-99)	56 (52-59)	6 (4-9)	99.6 (98-100)
<5%	9 (1.2)	749 (98.8)	67 (47-83)	88 (85-90)	15 (9-22)	99 (98-100)
Total	27 (3.1)	847 (96.9)	-	-	-	-

PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval, LVEF = left ventricular ejection fraction

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 76-99), specificity was 56% (95% CI 52-59), positive predictive value was 6% (95% CI 4-9), and negative predictive value was 99.6% (95% CI 98-100). 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 for LVEF<45% into true negatives (see Central Illustration). Supplement File D demonstrates the diagnostic rule derived from the model including ECG.



Central illustration. Reclassification of the risk of LVEF<45% when including "abnormal ECG based on LASSO analysis" and heart rate in childhood cancer survivors at risk of cardiomyopathy.

DISCUSSION

Our study in a nationwide cohort of ≥5-years childhood cancer survivors aimed at presenting evidence for ECG examination during cardiomyopathy surveillance. Our study is the first in demonstrating that complete left bundle branch block, left heart axis, left atrial dilatation, Cornell's Criteria for LV hypertrophy and heart rate are most strongly associated with clinically relevant myocardial dysfunction in survivors exposed to cardiotoxic cancer treatment. All these ECG abnormalities have been previously associated with decreased myocardial function in the general population[17,33]. We also found that the prevalence of ECG abnormalities increased with lower LVEF and that not all prevalent ECG abnormalities (such as Q waves) were useful to detect LV dysfunction. Furthermore, we have demonstrated that a diagnostic rule including four ECG abnormalities constituting "abnormal ECG based on LASSO analysis" and heart rate has potential to rule-out LVEF<45% in survivors at risk of cardiomyopathy, as it yielded a high negative predictive value and reasonable specificity of 56%. Such a strategy may aid in reducing echocardiographic examinations with minimal risk of missing survivors with a therapeutically relevant LVEF (see Central Illustration). Finally, ECG examination seemed unsuitable to detect, and thereby rule out, a slightly abnormal LVEF<54/52%.

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[16,40] 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 of future heart failure[41,42]. Although we did not find an association of these specific ECG abnormalities with LV dysfunction, follow-up of survivors with these ischemic findings may be warranted for other reasons such as preventive programs focusing on vascular or ischemic heart disease.

Another approach to refine the surveillance strategy is to identify the survivors with the highest risk of developing cardiomyopathy. Our results (Table D in supplements) indicated that ECG abnormalities are more likely to follow cardiac dysfunction with increased prevalence, than that they are predecessors of it. This would also explain why the model including ECG data was less informative for ruling-out LVEF<54% in females and <52% in males, and may also explain previous reports on some of the variability in sensitivity of ECG abnormalities for various degrees of LV dysfunction[20,21]. Thus, it may be that the more ECG abnormalities a person has, the more likely and severe the degree of

LV dysfunction is. Previous reports suggested that QTc time aids in the identification of survivors who will develop myocardial dysfunction[34]. In our cohort, the median QTc time in survivors with a mildly reduced LVEF (45% to 52/54%) was similar to those with normal LVEF and therefore does not seem to reflect a possible prediction of cardiac dysfunction, nor did the QTc time reflect the presence of a LVEF <45%.

We replicate results from the St Jude Lifetime Study (SJLS) in 2,715 survivors showing that ECG abnormalities mainly occurred in survivors exposed to heart RT[6]. We demonstrated that their rate is significantly higher compared to 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 clearly contributed to these rates. Furthermore, the relatively high numbers of high R-waves left 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 remodeling[43].

Study limitations

Besides the strengths of our study where we provided detailed information on ECG abnormalities in survivors at risk of cardiotoxicity, some limitations need to be considered. We could not evaluate the presence or absence of major ECG abnormalities in all 1,610 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[44] which enabled very precise measurements of the ECG with good or excellent inter-observer agreement. As a result, more ECG abnormalities such as Q-waves may have been detected in survivors as well as in siblings. Regarding the diagnostic value of ECG, validation of our results remains an important part of future research as our analysis included few events.

ECG examination is a relatively cheap, widely available and easy tool to assess the electrical function of the heart. Future research, such as clinical utility analysis[45], is needed to establish whether ECG patterns are useful to exclude survivors from echocardiographic examination. Whether echocardiography can be deferred for longer intervals remains unknown. Also, the association between specific ECG abnormalities and future cardiac diseases[15-17] needs further exploration in survivors. Recent studies demonstrated that application of artificial intelligence could open up new possibilities of ECG in the detection of asymptomatic left ventricular dysfunction[46,47]. As already demonstrated for incorporating the findings of a normal or slightly abnormal LVEF during follow-up in a

model to predict future LV dysfunction in a 10 year further follow-up[48], a similar finding of absence or presence of ECG abnormalities during follow-up could refine the prediction of future cardiac events in survivors.

CONCLUSION

Specific ECG abnormalities are clearly associated with worse myocardial function in survivors at risk of cardiomyopathy. The additions of a composite of ECG abnormalities and heart rate to a diagnostic model predicting a therapeutically relevant LVEF of <45% may help to reduce echocardiographic examinations in survivors at risk of cardiomyopathy.

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SUPPLEMENTAL MATERIAL

A. Additional information on cancer treatment variables

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

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

D. Association between ECG and systolic function – additional results

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

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

	Participant n=1,608	Nonparticipant 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*
18-29 years	33	33*
30-39 years	37	40*
≥40 years	29	26*
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

*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	All n=1,381*	Potentially cardiotoxic therapy n=155	Only anthracyclines or mitoxantrone n=809	Only heart RT n=158	Both anthracyclines/ mitoxantrone and heart RT 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]

	Siblings	Survivors				
	n=272	All n=1,381*	Potentially cardiotoxic therapy n=155	Only anthracyclines or mitoxantrone n=809	Only heart RT n=158	Both anthracyclines/ mitoxantrone and heart RT n=255
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
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

D. Association between ECG and systolic function – additional results

Comparison of the prevalence of the separate major and minor ECG abnormalities between survivors 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] unadjusted comparison with survivors who have a normal LVEF demonstrated a p-value <0.05

[b] comparison with survivors who have a 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

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)[b]	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)*	*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] Adjusted for sex, age at diagnosis, age at ECG and dose of anthracycline, mitoxantrone and heart RT.

AIC=Akaike information criterion, CI=confidence interval, ECG=electrocardiography, LEVF = left ventricular ejection fraction, OR = odds ratio

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

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

Diagnostic rule derived from model 2

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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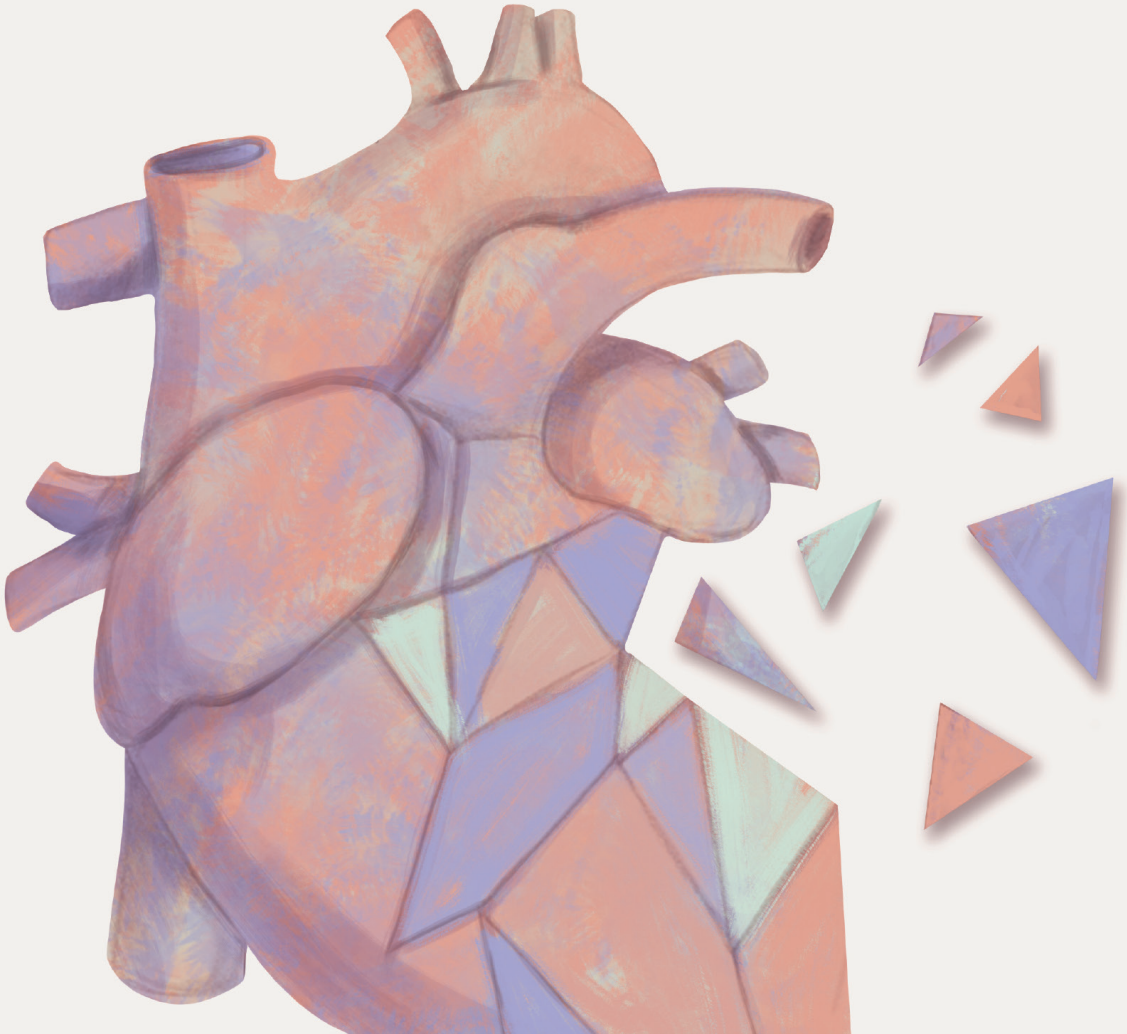

CHAPTER 5

Primary cardioprotection

5.1

DEXRAZOXANE FOR PREVENTING OR REDUCING CARDIOTOXICITY IN ADULTS AND CHILDREN WITH CANCER RECEIVING ANTHRACYCLINES

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Cochrane Database Syst Rev. 2022 Sep 27;9(9):CD014638

ABSTRACT

Background - This review is the third update of a previously published Cochrane Review. The original review, looking at all possible cardioprotective agents, was split and this part now focuses on dexrazoxane only.

Anthracyclines are effective chemotherapeutic agents in the treatment of numerous malignancies. Unfortunately, their use is limited by a dose-dependent cardiotoxicity. In an effort to prevent or reduce this cardiotoxicity, different cardioprotective agents have been studied, including dexrazoxane.

Objectives - To assess the efficacy of dexrazoxane to prevent or reduce cardiotoxicity and determine possible effects of dexrazoxane on antitumour efficacy, quality of life and toxicities other than cardiac damage in adults and children with cancer receiving anthracyclines when compared to placebo or no additional treatment.

Search methods - We searched CENTRAL, MEDLINE and Embase to May 2021. We also handsearched reference lists, the proceedings of relevant conferences and ongoing trials registers.

Selection criteria - Randomised controlled trials (RCTs) in which dexrazoxane was compared to no additional therapy or placebo in adults and children with cancer receiving anthracyclines.

Data collection and analysis - Two review authors independently performed study selection, data extraction, risk of bias and GRADE assessment of included studies. We analysed results in adults and children separately. We performed analyses according to the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results - For this update, we identified 548 unique records. We included three additional RCTs: two paediatric and one adult. Therefore, we included a total of 13 eligible RCTs (five paediatric and eight adult). The studies enrolled 1252 children with leukaemia, lymphoma or a solid tumour and 1269 participants, who were mostly diagnosed with breast cancer.

In adults, moderate-quality evidence showed that there was less clinical heart failure with the use of dexrazoxane (risk ratio (RR) 0.22, 95% confidence interval (CI) 0.11 to 0.43; 7 studies, 1221 adults). In children, we identified no difference in clinical heart failure risk between treatment groups (RR 0.20, 95% CI 0.01 to 4.19; 3 studies, 885 children; low-quality evidence). In three paediatric studies assessing cardiomyopathy/

heart failure as the primary cause of death, none of the children had this outcome (1008 children, low-quality evidence). In the adult studies, different definitions for subclinical myocardial dysfunction and clinical heart failure combined were used, but pooled analyses were possible: there was a benefit in favour of the use of dexrazoxane (RR 0.37, 95% CI 0.24 to 0.56; 3 studies, 417 adults and RR 0.46, 95% CI 0.33 to 0.66; 2 studies, 534 adults, respectively, moderate-quality evidence). In the paediatric studies, definitions of subclinical myocardial dysfunction and clinical heart failure combined were incomparable, making pooling impossible. One paediatric study showed a benefit in favour of dexrazoxane (RR 0.33, 95% CI 0.13 to 0.85; 33 children; low-quality evidence), whereas another study showed no difference between treatment groups (Fischer exact P = 0.12; 537 children; very low-quality evidence).

Overall survival (OS) was reported in adults and overall mortality in children. The meta-analyses of both outcomes showed no difference between treatment groups (hazard ratio (HR) 1.04, 95% 0.88 to 1.23; 4 studies; moderate-quality evidence; and HR 1.01, 95% CI 0.72 to 1.42; 3 studies, 1008 children; low-quality evidence, respectively). Progression-free survival (PFS) was only reported in adults. We subdivided PFS into three analyses based on the comparability of definitions, and identified a longer PFS in favour of dexrazoxane in one study (HR 0.62, 95% CI 0.43 to 0.90; 164 adults; low-quality evidence). There was no difference between treatment groups in the other two analyses (HR 0.95, 95% CI 0.64 to 1.40; 1 study; low-quality evidence; and HR 1.18, 95% CI 0.97 to 1.43; 2 studies; moderate-quality evidence, respectively). In adults, there was no difference in tumour response rate between treatment groups (RR 0.91, 95% CI 0.79 to 1.04; 6 studies, 956 adults; moderate-quality evidence). We subdivided tumour response rate in children into two analyses based on the comparability of definitions, and identified no difference between treatment groups (RR 1.01, 95% CI 0.95 to 1.07; 1 study, 206 children; very low-quality evidence; and RR 0.92, 95% CI 0.84 to 1.01; 1 study, 200 children; low-quality evidence, respectively). The occurrence of secondary malignant neoplasms (SMN) was only assessed in children. The available and worst-case analyses were identical and showed a difference in favour of the control group (RR 3.08, 95% CI 1.13 to 8.38; 3 studies, 1015 children; low-quality evidence). In the best-case analysis, the direction of effect was the same, but there was no difference between treatment groups (RR 2.51, 95% CI 0.96 to 6.53; 4 studies, 1220 children; low-quality evidence).For other adverse effects, results also varied. None of the studies evaluated quality of life.

If not reported, the number of participants for an analysis was unclear.

Authors' conclusions - Our meta-analyses showed the efficacy of dexrazoxane in preventing or reducing cardiotoxicity in adults treated with anthracyclines. In children, there was a difference between treatment groups for one cardiac outcome (i.e. for one of the definitions used for clinical heart failure and subclinical myocardial dysfunction combined) in favour of dexrazoxane. In adults, no evidence of a negative effect on tumour response rate, OS and PFS was identified; and in children, no evidence of a negative effect on tumour response rate and overall mortality was identified. The results for adverse effects varied. In children, dexrazoxane may be associated with a higher risk of SMN; in adults this was not addressed. In adults, the quality of the evidence ranged between moderate and low; in children, it ranged between low and very low. Before definitive conclusions on the use of dexrazoxane can be made, especially in children, more high-quality research is needed.

We conclude that if the risk of cardiac damage is expected to be high, it might be justified to use dexrazoxane in children and adults with cancer who are treated with anthracyclines. However, clinicians and patients should weigh the cardioprotective effect of dexrazoxane against the possible risk of adverse effects, including SMN, for each individual.

For children, the International Late Effects of Childhood Cancer Guideline Harmonization Group has developed a clinical practice guideline.

BACKGROUND

Description of the condition

Anthracyclines – that is, doxorubicin, epirubicin, idarubicin and daunorubicin – are drugs used in chemotherapy for the treatment of cancer. They are widely used to treat solid tumours and leukaemia in both adults and children. However, their use is limited because treatment with anthracyclines is associated with myocardial damage (Bonadonna 1969; Leerink 2020; Lefrak 1973).

Myocardial damage may lead to subclinical myocardial dysfunction, which is diagnosed by an imaging modality in people without symptoms. This may lead to clinical heart failure, which is a combination of myocardial dysfunction and the presence of related symptoms. Heart failure is one of the most severe longterm adverse effects in childhood cancer survivors (CCSs) and is associated with increased mortality (Fidler 2017; Mertens 2008). Heart transplantation is the only remaining treatment option for end-stage heart failure.

There is wide variation in the reported frequency of both subclinical myocardial dysfunction and clinical heart failure. In children, the prevalence of subclinical myocardial dysfunction at a median follow-up time of up to 23 years after cancer diagnosis or cardiotoxic cancer treatment is more than 56% (Kremer 2002a; Merkx 2021). The cumulative incidence of clinical heart failure can be as high as 16% (0.9 to 40 years after treatment, depending on the specific study) (Feijen 2019b; Kremer 2002b). The risk of subclinical myocardial dysfunction and clinical heart failure depends on the type of anthracycline used and increases with higher cumulative and peak doses (Armstrong 2015; Feijen 2019a; Feijen 2019b; Mulrooney 2020; Van Dalen 2010; Van Dalen 2016). Other important cancer treatment risk factors are radiation therapy involving the heart region, and the use of cyclophosphamide and mitoxantrone (Feijen 2019b). In addition, female sex, existing heart disease, a younger age at diagnosis and presence of traditional cardiovascular risk factors may play a role in the development of heart failure (Chellapandian 2019; Chow 2015; Mulrooney 2020; Van der Pal 2012).

Researchers have investigated whether anthracyclines can be omitted from the treatment regime without reducing survival. A study by Pritchard-Jones and colleagues, which included a subgroup of children with a Wilms tumour, showed that anthracyclines could safely be excluded from the treatment of this subgroup (Pritchard-Jones 2015). However, when anthracyclines cannot be avoided (Van Dalen 2014), clinicians may have a clinical

dilemma as they balance the efficacy of higher cumulative doses of anthracyclines against the cardiotoxicity associated with these higher doses. In an effort to prevent or reduce this cardiotoxicity, extensive research has been devoted to the identification of methods or drugs capable of ameliorating the toxicity. Several less cardiotoxic anthracycline analogues have been developed, including liposomal anthracyclines (Batist 2001; Fojtu 2017; Hori 2017; Muggia 1991; Muggia 1997; Van Dalen 2010), and the cumulative and peak doses of anthracycline therapy have been reduced (Legha 1982; Lipshultz 1998; Loeffen 2018; Van Dalen 2016; Von Hoff 1979). Despite these efforts, anthracycline-induced cardiotoxicity (AIC) remains an issue.

Description of the intervention

A different approach to prevent or reduce AIC is the use of cardioprotective agents, of which dexrazoxane (also known as Cardioxane, ICRF-187; Zinecard, ADR-529) is the most widely investigated drug. An important question regarding any cardioprotective intervention during anthracycline therapy is whether the cardioprotective drug can reduce any myocardial damage caused by anthracyclines without affecting the antitumour efficacy and without causing other adverse effects, such as alopecia, nausea, vomiting and anaemia.

How the intervention might work

We do not understand exactly the mechanism of how anthracyclines cause myocardial damage. It may be due to lipid peroxidation and the generation of free radicals by anthracyclineiron complexes. The myocardium is particularly vulnerable to injury from free radicals as it has a lower level of protective enzymes, such as superoxide dismutase, than other tissues (Keizer 1990; Myers 1998). As dexrazoxane chelates iron, it may decrease cardiotoxicity by preventing the formation of free radicals (Gammella 2014). In recent years, interest has grown in another possible contributor to AIC; namely, topoisomerase 2β (TOP2B). This enzyme is highly expressed in cardiomyocytes and causes apoptosis when bound to anthracycline. Animal studies have also suggested that dexrazoxane may prevent cardiotoxicity via inhibition of TOP2B (Deng 2014; Lyu 2007).

Why it is important to do this review

The risk of developing heart failure remains a lifelong threat, especially to children who would otherwise have a long life expectancy after successful treatment for cancer. Therefore, the prevention or reduction of AIC is crucial.

This is the third update of the systematic review on cardioprotective interventions during anthracycline therapy. The review has been split and this update focuses on dexrazoxane alone. Since the last update (Van Dalen 2011), new evidence on dexrazoxane has become available and is included in this update. A second updated review will focus on other cardioprotective interventions.

OBJECTIVES

To assess the efficacy of dexrazoxane to prevent or reduce cardiotoxicity and determine possible effects of dexrazoxane on antitumour efficacy, quality of life and toxicities other than cardiac damage in adults and children with cancer receiving anthracyclines when compared to placebo or no additional treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults and children with cancer who received anthracycline chemotherapy.

Types of interventions

- Intervention: anthracycline therapy together with dexrazoxane.
- Control: anthracycline therapy with or without a placebo.

In the design of the study (i.e. according to protocol), it should have been the intention to treat (ITT) both the intervention and control groups with the same cumulative anthracycline dose. The median or mean cumulative anthracycline dose participants actually received should not have differed between the treatment groups by 100 mg/m2 or more of body

surface area. Any chemotherapy other than anthracyclines and radiotherapy involving the heart should have been the same in both treatment groups.

Types of outcome measures

Primary outcomes

- Heart failure:
  - clinical heart failure (as defined by the authors; including death caused by heart failure)
  - clinical heart failure (as defined by the authors; including death caused by heart failure) and subclinical myocardial dysfunction (defined as either abnormalities in cardiac function measured by imaging (echocardiography, radionuclide ventriculography or cardiac magnetic resonance imaging) or histological abnormalities scored by the Billingham score (Billingham 1978) on endomyocardial biopsy) combined
- Overall survival (OS) or overall mortality

Secondary outcomes

- Progression-free survival (PFS)
- Tumour response rate (for adults, defined as the number of complete and partial remissions; for children, defined as the number of complete remissions)
- Quality of life (QoL, as defined by the authors)
- Toxicities other than cardiac damage (such as secondary malignant neoplasms (SMN), alopecia, nausea, vomiting, stomatitis, diarrhoea, fatigue, anaemia, leukopenia, thrombocytopenia)

Search methods for identification of studies

We imposed no language restrictions.

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 1) in the Cochrane Library (searched 7 May 2021);
- MEDLINE (PubMed) (from 1966 to 7 May 2021); and
- Embase (Ovid) (from 1980 to 7 May 2021).

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are detailed in the appendices (Appendix 1, Appendix 2, Appendix 3). These searches included the National Institutes of Health and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Searching other resources

We located information about trials not listed in CENTRAL, MEDLINE or Embase, either published or unpublished, by searching the reference lists of included articles and review articles. In addition, we searched the conference proceedings of the International Society for Paediatric Oncology (SIOP) and the American Society of Clinical Oncology (ASCO) from 1998 to 2020 (see Appendix 4 for search strategies).

Data collection and analysis

Selection of studies

After performing the search strategy described previously, two review authors independently identified studies meeting the inclusion criteria. We obtained the full-text articles for any study seemingly meeting the inclusion criteria based on the title, abstract, or both, for closer inspection. We resolved any discrepancies by discussion or, when this was not possible, by thirdparty arbitration. We clearly stated the details of the reasons for exclusion of any study considered for the review. We included a flow diagram of the selection of studies (Figure 1). When multiple reports of one study were identified, we collated the full-text results.

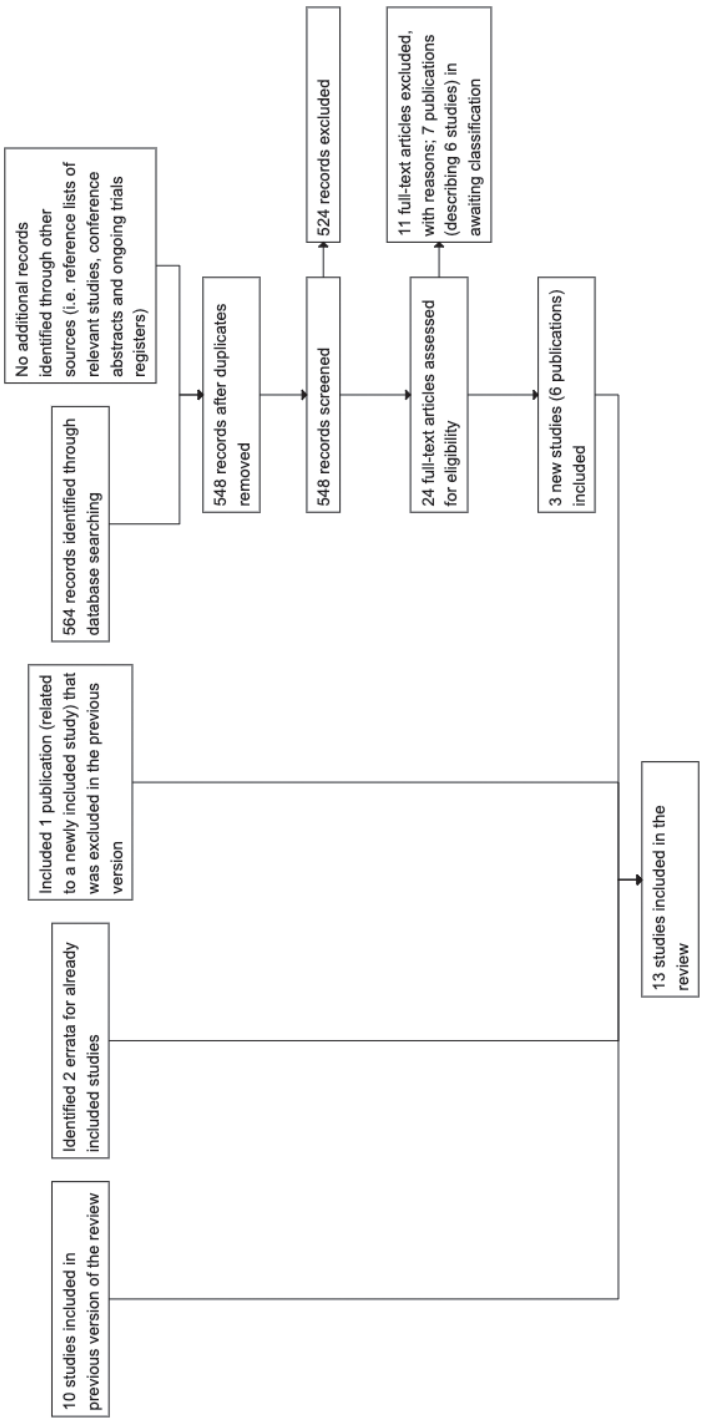

Figure 1. Flow diagram of selection of studies

Data extraction and management

Two review authors independently performed the data extraction using standardised data collection forms.

We extracted the characteristics of the participants (for example: age, type of malignancy, stage of disease), intervention (for example: dose, timing), outcome measures, length of follow-up, details of funding sources and the declaration of interests for each included study. To inform interpretation of the findings, we assessed the similarity of the experimental groups at baseline regarding the most important prognostic indicators (that is, age, prior cardiotoxic therapy, prior cardiac dysfunction and stage of disease). We resolved any discrepancies between review authors by discussion or, when this was not possible, by third-party arbitration.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies (i.e. selection bias, performance bias, detection bias (for each outcome separately), attrition bias (for each outcome separately), reporting bias and other potential sources of bias). We used the risk of bias items as described in the module of Cochrane Childhood Cancer (Module CCG), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved discrepancies between review authors by discussion and needed no third-party arbitration. We took into account the risk of bias in the included studies in the interpretation of the review's results.

Measures of treatment effect

We analysed dichotomous variables using risk ratios (RR). For the assessment of survival, we used the generic inverse variance function of the Review Manager 5 software (Review Manager 2020) to combine logs of the hazard ratios (HRs). Parmar's method was used to extract the log of the HR and its standard error (SE) from survival curves (Parmar 1998) for the studies of Marty 2006 and Speyer 1992. We digitised the published Kaplan-Meier survival curves and noted the minimum and maximum duration of follow-up (Guyot 2012), which are required for Parmar's method. We performed the required calculations in Stata 9 (Stata 2005), using a specially written program, which yielded the reported log(HR) and variance when used on the data presented in table V of Parmar 1998. We presented all results with the corresponding 95% confidence interval (CI).

Unit of analysis issues

Unit of analysis issues were not applicable.

Dealing with missing data

When relevant data regarding study selection, data extraction and risk of bias assessment were missing, we attempted to contact the study authors to retrieve the missing data. If possible, we extracted data by allocated group, irrespective of compliance with the allocated intervention, in order to allow an intentionto-treat analysis. If outcome assessments were not available for all participants, we performed an available-case analysis and, if possible, also a best-case and worst-case analysis. The availablecase analysis only includes participants who had an outcome assessment. The best-case analysis includes all participants and usually assumes that participants without an outcome assessment did not develop the outcome (for example, heart failure). The worstcase analysis includes all participants and usually assumes that all participants without an outcome assessment developed the outcome. However, for example, for tumour response rate (i.e. number of participants with a remission) this is the opposite: due to the nature of this outcome, 'best case' here means that the participant does have the outcome.

Assessment of heterogeneity

We assessed heterogeneity by both visual inspection of forest plots and by a formal statistical test for heterogeneity; namely, the I^2 statistic (we considered $I^2 > 50\%$ to represent substantial heterogeneity) (Higgins 2011). If we detected substantial heterogeneity, we explored possible reasons for the occurrence of heterogeneity.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studies section, we planned to assess reporting bias by constructing a funnel plot when there was a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis); without this number, the power of the test is too low to distinguish chance from real asymmetry (Higgins 2011). Since all meta-analyses included fewer than 10 studies, this was not applicable.

Data synthesis

We entered data into the Review Manager 5 software provided by Cochrane (Review Manager 2020; RevMan Web 2021). We performed analyses according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed a meta-analysis if two or more comparable studies were identified. If this was not the case, we summarised results descriptively. For outcomes where only one study was available and we were unable to calculate a RR as one of the treatment groups experienced no events, we used Fischer's exact test instead (www.graphpad.com/quickcalcs/contingency1.cfm).

Subgroup analysis and investigation of heterogeneity

We planned to analyse data separately for children and adults and different types of tumour (i.e. leukaemia and solid tumours) if there were a sufficient number of trials of adequate size. However, this was not possible for different tumour types, as all adult participants were diagnosed with a solid tumour and data available for children were limited.

Sensitivity analysis

For all outcomes for which pooling was possible, we performed sensitivity analyses for all risk of bias items separately (i.e. excluding studies with a high risk of bias and studies for which the risk of bias was unclear, and comparing the results of studies with a low risk of bias with the results of all available studies; we only performed sensitivity analyses if at least two studies remained in the analysis after exclusion of the studies with a high or unclear risk of bias).

Summary of findings and assessment of the certainty of the evidence

We prepared summary of findings tables based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021*),* and using GRADEpro software (GRADEpro GDT). We presented the following outcomes: heart failure, OS, PFS, tumour response rate, QoL and secondary malignant neoplasms (SMN). Two review authors independently assessed the quality of the evidence (i.e. very low, low, moderate or high quality) for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account study limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias.

RESULTS

Description of studies

Results of the search

At the start of the third update, we split the original review to address dexrazoxane separately. Consequently, the search results below only discuss studies on dexrazoxane.

Up to and including the second update, we included 10 studies that addressed dexrazoxane: DFCI 95-01 (study ID was Lipshultz 2004 in the 2011 review update); Galetta 2005; Lopez 1998; Marty 2006; P9425 (study ID was Schwartz 2009 in the 2011 review update); Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996; Wexler 1996. An overview of the full search results and study flow for the second review update can be found in Van Dalen 2011 and in Appendix 5.

For the third update, our searches in CENTRAL, MEDLINE and Embase yielded 564 records. After removing duplicates, we screened the titles or abstracts (or both) of 548 records. We excluded 524 records as they clearly did not meet the inclusion criteria. We obtained the remaining 24 full-text articles and assessed these for inclusion. We identified three new studies (six publications) eligible for inclusion: P9404, P9426, and Sun 2016. Of the remaining 18 publications, five described five new studies that did not meet the eligibility criteria for inclusion in the review. We added seven publications (six studies) to the studies awaiting classification, either because they were conference abstracts, ongoing trial registry entries of studies for which some preliminary results are already available in conference abstracts (but no fulltext publications are available yet) or they are awaiting translation. The final six publications were associated with included studies; we collated these with their respective studies.

We identified no additional eligible studies after scanning the reference lists of relevant articles and conference proceedings. We identified errata for two already included studies (P9425; Speyer 1992). Furthermore, we checked (26 May 2021) if new information was available on the studies listed in the Characteristics of ongoing studies and the Characteristics of studies awaiting classification tables in the second update of this review. For two of the three ongoing studies previously listed, results were now available and identified in the electronic database searches of this update. Therefore, only one ongoing study remains (Characteristics of ongoing studies). For the studies awaiting classification, no new information was available. Finally, cardiac data became available for the P9426 study, so we could include long-term follow-up data on other outcomes for the third update (Tebbi 2007; previously excluded).

In order to comply with Cochrane policy, 12 publications labelled as 'excluded studies' in the previous versions of this review, which were associated with various included studies, are now collated with their respective included studies.

In summary, we included a total of 13 studies in the third update of this systematic review. See Figure 1 for a flow diagram of the selection of studies.

Included studies

Of the 13 included RCTs, seven RCTs addressed dexrazoxane solely in adults (Galetta 2005; Marty 2006; Speyer 1992; Sun 2016; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996), four RCTs investigated the effects of dexrazoxane solely in children (DFCI 95-01; P9404; P9425; P9426), and two RCTs included both children and adults (Lopez 1998; Wexler 1996). We categorised the study of Wexler 1996 as paediatric since the age at diagnosis was maximum 24 years (range 4 to 24). We included the study of Lopez 1998 in the adult category as the median age at diagnosis was 50+ years (range 14 to 75). The same study group conducted three of the studies: P9404 investigated leukaemia and nonHodgkin lymphoma; P9425 investigated intermediate- and highrisk Hodgkin lymphoma; and P9426 investigated low-risk Hodgkin lymphoma. The Swain studies both investigated dexrazoxane for women with breast cancer but investigated different stages of disease and applied different treatments.

The baseline characteristics of the participants in these studies are summarised below; more detailed information can be found in the Characteristics of included studies table.

Adults

The total number of participants in the eight adult studies was 1269 (622 in the dexrazoxane groups and 647 in the control groups). In five studies, the control groups did not receive a cardioprotective intervention (N = 327) and in three studies, the control group received a placebo (N = 340) (Sun 2016; Swain 1997a(088001); Swain 1997a(088006)). All participants were diagnosed with a solid tumour of which the majority had advanced breast cancer. Participants were treated with doxorubicin in three studies (Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)), with epirubicin in four studies (Galetta 2005; Lopez 1998; Sun 2016; Venturini 1996), and with either epirubicin or doxorubicin in one study (Marty 2006). The ratio of dexrazoxane to anthracycline dose varied between studies and was ether 6.25:1, 10:1 or 20:1. In four studies, adults in the dexrazoxane groups and control groups received comparable cumulative anthracycline doses (Lopez 1998;

Marty 2006; Sun 2016; Venturini 1996); in one study, the mean cumulative anthracycline was 150 mg/m2 higher in thedexrazoxane group compared to the control group (Speyer 1992); and in three studies, it was unclear whether cumulative anthracycline doses were comparable (Galetta 2005; Swain 1997a(088001); Swain 1997a(088006)).

Children

The total number of participants in the five paediatric studies was 1252 (632 in the dexrazoxane groups and 620 in the control groups). None of the children in the control groups received a cardioprotective intervention or placebo. One study included children with a solid tumour, including a Ewing sarcoma family tumour (Wexler 1996). Two studies included children with Hodgkin lymphoma (P9425; P9426). One study included children with leukaemia (DFCI 95-01), and another study included children with leukaemia or non-Hodgkin lymphoma (P9404). All studies used doxorubicin for cancer treatment. The ratio of dexrazoxane to anthracycline dose varied between studies and was either 10:1 (DFCI 95-01; P9404; P9425; P9426), or 20:1 (Wexler 1996). In two studies, it was unclear if children in the intervention and control groups received similar cumulative anthracycline doses (DFCI 95-01; P9425). In two studies, the cumulative anthracycline dose was not mentioned, but it was either stated that all children received the same cumulative dose (P9404), or that the received dose was in high compliance with the prescribed dose (P9426). In one study, the median cumulative anthracycline dose was 100 mg/ m2 higher in thedexrazoxane group as compared to the control group (Wexler 1996).

Excluded studies

In this review update, there are eight excluded studies (Getz 2019; Li 2013; Massida 1997; Neto 2006; Paiva 2005; Rabinovich 2012; Tap 2019; Wang 2020). The primary reasons for exclusion were: ineligible study design (three studies); ineligible intervention or control (three studies); and ineligible outcome measurement (e.g. no cardiac outcomes or cardiac function not measured by echocardiography or radionuclide ventriculography).

Risk of bias in included studies

See the risk of bias section of the Characteristics of included studies table and Figure 2 for detailed judgements of risk of bias for each included study and the support for the judgements made.

Allocation

For evaluating selection bias, we assessed random sequence generation and allocation concealment.

Adults

Two studies applied both random sequence generation and concealed treatment allocation, and thus we assessed the risk of selection bias as low (Swain 1997a(088001); Swain 1997a(088006)). For the six remaining studies in adults, the risk of selection bias was unclear: in three studies, both random sequence generation and allocation concealment were unclear (Galetta 2005; Lopez 1998; Speyer 1992); in one study, random sequence generation was applied, but allocation concealment was unclear (Sun 2016); and in two studies, treatment allocation was concealed, but random sequence generation was unclear (Marty 2006; Venturini 1996).

Children

One study applied both random sequence generation and concealed treatment allocation, and thus we assessed the risk of selection bias as low (DFCI 95-01). For the four remaining studies in children, the risk of selection bias was unclear: in three studies, both random sequence generation and allocation concealment were unclear (P9404; P9425; P9426); and in one study, random sequence generation was applied, but allocation concealment was unclear (Wexler 1996).

Blinding

For evaluating performance bias, we assessed blinding of participants and personnel. For evaluating detection bias, we scored blinding of outcome assessors separately for all outcomes with the exception of overall survival/overall mortality and adverse effects other than cardiac damage and diagnosed by laboratory tests. Since blinding is not relevant for these outcomes, we judged the risk of bias as low. Not all studies assessed all outcomes.

Adults

The risk of performance bias was low in two studies (Swain 1997a(088001); Swain 1997a(088006)), high in five studies (Galetta 2005; Lopez 1998; Marty 2006; Speyer 1992; Venturini 1996), and unclear in one study (Sun 2016). For clinical heart failure, the risk of

detection bias was low in five studies (Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996), and unclear in two studies (Lopez 1998; Sun 2016). For clinical heart failure and subclinical myocardial dysfunction combined, the risk of detection bias was low in five studies (Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996), and unclear in one study (Lopez 1998). For tumour response rate, the risk of detection bias was low in two studies (Swain 1997a(088001); Swain 1997a(088006)), and unclear in four studies (Lopez 1998; Marty 2006; Speyer 1992; Venturini 1996). For progression-free survival (PFS), the risk of detection bias was low in two studies (Swain 1997a(088001); Swain 1997a(088006)), and unclear in two studies (Marty 2006; Speyer 1992). For adverse effects other than cardiac damage and those not diagnosed by a laboratory test, the risk of detection bias was low in two studies (Swain 1997a(088001); Swain 1997a(088006)), and unclear in five studies (Lopez 1998; Marty 2006; Speyer 1992; Sun 2016; Venturini 1996).

Children

The risk of performance bias was high in all five studies. For clinical heart failure, the risk of detection bias was low in one study (DFCI 95-01), and unclear in two studies (P9404; P9425). For cardiomyopathy/heart failure as primary cause of death, the risk of detection bias was low in all studies assessing this outcome (P9404; P9425; P9426). For tumour response rate, the risk of detection bias was low in one study (DFCI 95-01), and unclear in the other study (P9425). For clinical heart failure and subclinical myocardial dysfunction combined (P9404; Wexler 1996), and adverse effects other than cardiac damage and those not diagnosed by laboratory tests (DFCI 95-01; P9404; P9425; P9426), the risk of detection bias was unclear in all studies assessing these outcomes.

Incomplete outcome data

For evaluating attrition bias, we assessed incomplete outcome data for all outcomes separately. A maximum of 10% of participants with missing data in each treatment arm was acceptable. Not all outcomes were assessed by all studies.

Adults

We assessed the risk of attrition bias as low for clinical heart failure in all studies addressing the outcome (Lopez 1998; Marty 2006; Speyer 1992; Sun 2016; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996). For clinical heart failure and subclinical myocardial

dysfunction combined, the risk of attrition bias was low in four studies (Lopez 1998; Marty 2006; Swain 1997a(088001); Swain 1997a(088006)), high in one study (Venturini 1996), and unclear in one study (Speyer 1992). For overall survival (OS), the risk of attrition bias was high in one study (Marty 2006), and unclear in three studies (Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)). For tumour response rate, the risk of attrition bias was low for three studies (Lopez 1998; Speyer 1992; Venturini 1996), and high for three studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006)). For PFS, the risk of attrition bias was low in one study (Marty 2006), and unclear in three studies (Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)). For toxicities other than cardiac damage, the risk of attrition bias was low in five studies (Lopez 1998; Marty 2006; Speyer 1992; Sun 2016; Venturini 1996), and unclear in two studies (Swain 1997a(088001); Swain 1997a(088006)).

Children

For clinical heart failure, we assessed the risk of attrition bias as low in two studies (P9404; P9425), and high in one study (DFCI 95-01). The risk of attrition bias was high for clinical heart failure and subclinical myocardial dysfunction combined in both studies addressing this outcome (P9404; Wexler 1996). The risk of attrition bias was low for cardiomyopathy/ heart failure as primary cause of death (P9404; P9425; P9426), overall mortality (P9404; P9425; P9426), and secondary malignant neoplasms (SMN) (DFCI 95-01; P9404; P9425; P9426). For tumour response rate, the risk of attrition bias was low in one study (P9425), and unclear in the other study (DFCI 95-01). For toxicities other than cardiac damage with the exception of SMN, the risk of attrition bias was low in two studies (P9404; P9425), and high in one study (P9426).

Selective reporting

For evaluating reporting bias, we assessed selective reporting. The predefined expected outcomes were cardiotoxicity (clinical, asymptomatic or both) and overall survival.

Adults

We assessed the risk of reporting bias as low in six studies (Lopez 1998; Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996), and high in two studies (Galetta 2005; Sun 2016). For Galetta 2005, it should be noted that the primary objective of this study was to assess QT-dispersion on electrocardiogram (ECG), not to assess heart failure.

Children

We assessed the risk of reporting bias as low in four studies (P9404; P9425; P9426; Wexler 1996), and high in one study (DFCI 95-01).

Other potential sources of bias

For evaluating other potential sources of bias, we assessed the following items: block randomisation in unblinded trials, baseline imbalance between treatment groups related to outcome (prior cardiotoxic treatment (anthracyclines and cardiac irradiation), age, gender, stage of disease and prior cardiac dysfunction) and different lengths of follow-up between treatment arms.

Adults

The risk of other potential sources of bias was unclear for all included studies. For a detailed description of the different items, see the risk of bias section of the Characteristics of included studies table.

Children

The risk of other potential sources of bias was unclear for all included studies. For a detailed description of the different items, see the risk of bias section of the Characteristics of included studies table.

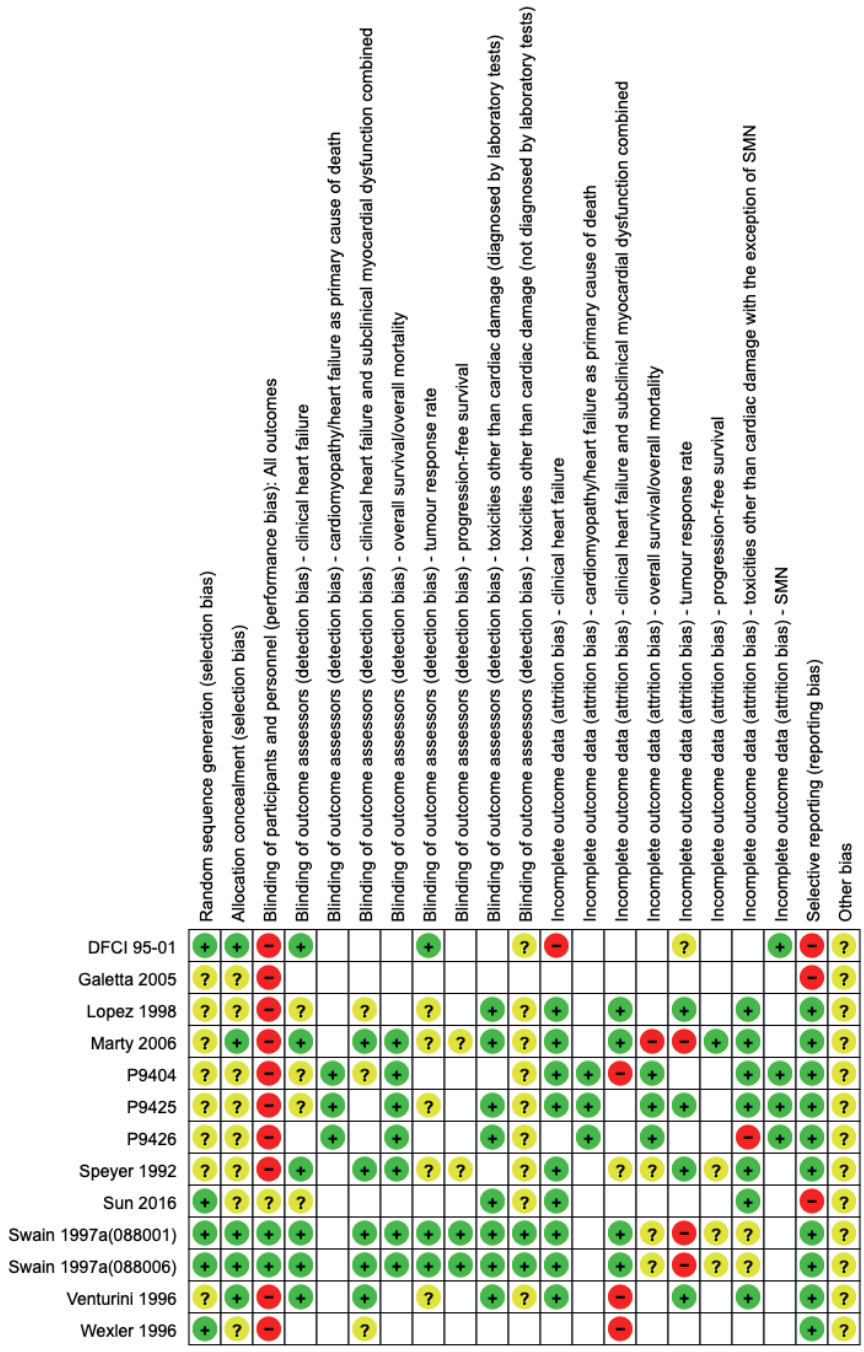

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (+= low risk of bias, - = high risk of bias, ? = unclear risk of bias)

Effects of interventions

See: Summary of findings 1 Dexrazoxane versus no cardioprotective intervention or placebo for preventing or reducing cardiotoxicity in adults with cancer receiving anthracyclines; Summary of findings 2 Dexrazoxane versus no cardioprotective intervention for preventing or reducing cardiotoxicity in children with cancer receiving anthracyclines

Not all articles allowed data extraction for all endpoints (see the Characteristics of included studies table for detailed descriptions of the extractable endpoints in each study).

Summary of findings Table 1. Dexrazoxane versus no cardioprotective intervention or placebo for preventing or reducing cardiotoxicity in adults with cancer receiving anthracyclines

Dexrazoxane compared with no cardioprotective intervention or placebo for preventing or reducing cardiotoxicity in adults with cancer receiving anthracyclines

Patient or population: adults with cancer receiving anthracyclines
Settings: hospital
Intervention: dexrazoxane
Comparison: no cardioprotective intervention or placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention or placebo	Dexrazoxane				
Clinical heart failure Available case analysis Follow-up ranged between 1 day and 5.1 years (nm for 5 studies)	107 per 1000[a]	24 per 1000 (12 to 46)	RR 0.22 (0.11 to 0.43)	1221 (7 studies)	⊕⊕⊕⊖ **Moderate**[b,c]	In 1 study, none of the participants developed clinical heart failure; the relative effect for that study was not estimable. The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment. In the worst-case analysis, there was unexplained heterogeneity (I^2 = 52%).
Clinical heart failure and subclinical myocardial dysfunction combined Comparable definitions; see Characteristics of included studies for exact definitions. Available-case analysis Follow-up nm	314 per 1000[a]	116 per 1000 (75 to 176)	RR 0.37 (0.24 to 0.56)	417 (3 studies)	⊕⊕⊕⊖ **Moderate**[c,d]	The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention or placebo	Dexrazoxane				
Clinical heart failure and subclinical myocardial dysfunction combined Comparable definitions; see Characteristics of included studies for exact definitions. Available-case analysis Follow-up ranged between 1 day and 5.1 years	312 per 1000[a]	144 per 1000 (103 to 206)	RR 0.46 (0.33 to 0.66)	534 (2 studies)	⊕⊕⊕⊖ **Moderate**[c,e]	The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment.
Overall survival (Illustrative comparative risks reported as number of alive participants) Follow-up ranged between 1 day and 5.1 years (nm for 2 studies)	233 per 1000[f]	219 per 1000 (166 to 277)	HR 1.04 (0.88 to 1.23)	Unclear (4 studies)	⊕⊕⊕⊖ **Moderate**[g,h]	
Progression-free survival Defined as time from first date of complete response, partial response or stable disease until the date progressive disease was first noticed (Illustrative comparative risks reported as number of participants without progressive disease) Follow-up nm	0 per 1000[i]	0 per 1000 (0 to 3)	HR 0.62 (0.43 to 0.90)	164 (1 study)	⊕⊕⊖⊖ **Low**[j,k]	All participants in the control group had progression at the end of follow-up, but as the GRADEpro software was not able to calculate the corresponding risk with an assumed risk of 0%, we used 0.0001% as the assumed risk in the control group instead.
Progression-free survival Defined as time to progression; starting point nm (Illustrative comparative risks reported as number of participants without progression) Follow-up nm	150 per 1000[l]	165 per 1000 (70-297)	HR 0.95 (0.64 to 1.40)	Unclear (1 study)	⊕⊕⊖⊖ **Low**[m,n]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention or placebo	Dexrazoxane				
Progression-free survival Defined as time from randomisation to progression either on or off treatment (Illustrative comparative risks reported as number of participants without progression) Follow-up ranged between 1 day and 5.1 years	100 per 1000[o]	66 per 1000 (37 to 107)	HR 1.18 (0.97 to 1.43)	Unclear (2 studies)	⊕⊕⊕⊖ **Moderate**[p,q]	
Tumour response rate Defined as number of complete or partial remissions Available-case analysis Follow-up ranged between 1 day and 5.1 years (nm for 4 studies)	533 per 1000[a]	485 per 1000 (421 to 554)	RR 0.91 (0.79 to 1.04)	956 (6 studies)	⊕⊕⊕⊖ **Moderate**[r,s]	Due to the nature of this outcome (number of participants with a remission), a high event rate is favourable. The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment.
Quality of life			No studies evaluated this outcome			
Secondary malignant neoplasms			No studies evaluated this outcome			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

Footnotes

CI: confidence interval, CTCAEv2: Common Terminology Criteria for Adverse Events, version 2, e.g.: for example, HR: hazard ratio, LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, MUGA: multigated acquisition scan, NCI: National Cancer institute, nm: not mentioned

P: P-value, RR: risk ratio

[a] The assumed risk is based on the overall prevalence in the control groups of the included studies.

[b] Unclear risk of selection bias in 5 (71%) studies, high risk of performance bias in 4 (57%) and unclear risk in 1 (14%) of the studies, unclear risk of detection bias in 2 (29%) studies, high risk of selective reporting in 1 (14%) study, unclear risk of other bias in all studies (downgraded 1 level).

[c] We did not downgrade for imprecision; the total number of events was fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook), but the effect was large and the 95% CI is small and below no effect.

[d] Unclear risk of selection and other bias in all studies, high risk of performance bias in all studies, unclear risk of detection bias in 1 (33%) study, high risk of attrition bias in 1 (33%) study (downgraded 1 level).

[e] Unclear risk of other bias in all studies (downgraded 1 level).

[f] The assumed risk is based on the approximate mean percentage of participants alive in the control groups at the final point of the survival curves presented in the included studies.

[g] Unclear risk of selection bias in 2 (50%) studies, high risk of performance bias in 2 (50%) studies, high risk of attrition bias in 1 (25%) study and unclear in 3 studies (75%), unclear risk of other bias in all studies (downgraded 1 level).

[h] We did not downgrade for imprecision; the number of events and total available participants in the 4 studies was unclear, but based on the maximum number of participants and the assumed baseline risk, we assumed that it was above 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook); the 95% CI includes no effect, but was small.

[i] The assumed risk is based on the percentage of participants without progression in the control group at the final point of the survival curve presented in the included study (see comments for more information).

[j] Unclear risk of selection bias, detection bias and other bias and a high risk of performance bias in the included study (downgraded 1 level).

[k] As this was a small study with a total number of events fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook) without a large effect, we downgraded 1 level, even though the 95% CI was below no effect.

[l] The assumed risk is based on the approximate percentage of participants without progression in the control group at the final point of the survival curve presented in the included study.

[m] Unclear risk of selection bias, detection bias, attrition bias and other bias and a high risk of performance bias in the included study (downgraded 1 level).

[n] As this was a small study with a total number of events fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook), we downgraded 1 level.

[o] The assumed risk is based on the approximate mean percentage of participants alive in the control groups at the final point of the survival curves presented in the included studies.

[p] Unclear risk of attrition and other bias in both studies (downgraded 1 level).

[q] We did not downgrade for imprecision; the number of events and available participants in the 2 studies was unclear, but based on the maximum number of participants and the assumed baseline risk we assumed that it was above 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook); the 95% CI includes no effect, but was small.

[r] Unclear risk of selection and detection bias in 4 (67%) studies, high risk of performance bias in 4 (67%) studies, high risk of attrition bias in 3 (50%) studies, unclear risk of other bias in all studies (downgraded 1 level).

[s] We did not downgrade for imprecision; the total number of events was more than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook); the 95%CI includes no effect, but was small.

Summary of findings Table 2. Dexrazoxane versus no cardioprotective intervention or placebo for preventing or reducing cardiotoxicity in children with cancer receiving anthracyclines

Dexrazoxane compared with no cardioprotective intervention for preventing or reducing cardiotoxicity in children with cancer receiving anthracyclines

Patient or population: children with cancer receiving anthracyclines

Settings: hospital

Intervention: dexrazoxane

Comparison: no cardioprotective intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention	Dexrazoxane				
Clinical heart failure Available-case analysis Follow-up ranged between 0.01 and 15 years (nm for 1 study)	5 per 1000[a]	1 per 1000 (0 to 19)	RR 0.20 (0.01 to 4.19)	885 (3 studies)	⊕⊕⊖⊖ **Low**[b,c]	In 2 studies, none of the participants developed clinical heart failure; the relative effect for those studies was not estimable. The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment.
Cardiomyopathy/heart failure primary cause of death Available-case analysis Follow-up ranged between 0 and 15.5 years	-	-	Not estimable (see comments)	1008 (3 studies)	⊕⊕⊖⊖ **Low**[c,d]	In all studies, none of the participants had cardiomyopathy/heart failure as the primary cause of death; the relative effect was not estimable. The available-case, best-case and worst-case analyses were identical, including the GRADE assessment.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention	Dexrazoxane				
Clinical heart failure and subclinical myocardial dysfunction combined Defined as (1) evidence of clinical congestive heart failure, (2) a reduction in LVEF as measured by MUGA to < 45% or (3) a decrease in LVEF as measured by MUGA of > 20 percentage points from baseline. Available-case analysis Follow-up nm for randomised participants	667 per 1000[a]	220 per 1000 (87 to 567)	RR 0.33 (0.13 to 0.85)	33 (1 study)	⊕⊕⊖⊖ **Low**[e,f]	The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment. Study participants were aged between 4 and 24 years, so not all paediatric patients (< 21 years).
Clinical heart failure and subclinical myocardial dysfunction combined Defined as clinical heart failure (no definition provided) or subclinical myocardial dysfunction defined as decreased LVFS; however, it was stated that toxicity was graded according to NCI CTCAEv2 criteria, grade 3 or higher but LVFS is not included in that definition. Best-case analysis Follow-up ranged between 0.01 and 15 years	-	-	Not estimable (see comments)	537 (1 study)	⊕⊖⊖⊖ **Very low**[g,h]	For this outcome definition, only one study was available in which one of the treatment groups experienced no events. Thus, we were not able to calculate a RR and we used Fischer's exact test instead (P = 0.12). Only a best-case analysis could be performed due to an unclear number of participants lost to follow-up.
Overall mortality (Reported as number of participants who died) Follow-up ranged between 0 and 15.5 years	130 per 1000[i]	131 per 1000 (95 to 179)	HR 1.01 (0.72 to 1.42)	1008 (3 studies)	⊕⊕⊖⊖ **Low**[c,d]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention	Dexrazoxane				
Progression-free survival	No studies evaluated this outcome					
Tumour response rate Defined as number of complete remissions (no definition of complete remission provided). Best-case analysis Follow-up median 2.7 years	950 per 1000[a]	960 per 1000 (903 to 1000)	RR 1.01 (0.95 to 1.07)	206 (1 study)	⊕⊖⊖⊖ **Very low**[h,j]	Due to the nature of this outcome (number of participants with a complete remission), a high event rate is favourable. Only a best-case analysis could be performed due to an unclear number of participants lost to follow-up.
Tumour response rate Defined as number of complete responses (i.e. disappearance of active Hodgkin lymphoma (gallium negative, ≥ 70% decrease in the sum of the products of the perpendicular diameters of measurable lesions, and negative bone marrow or bone scan if initially positive)). Available-case analysis Follow-up nm (median follow-up for participants without an event was 5.2 years).	939 per 1000[a]	864 per 1000 (789 to 949)	RR 0.92 (0.84 to 1.01)	200 (1 study)	⊕⊕⊖⊖ **Low**[h,k]	Due to the nature of this outcome (number of participants with a complete response), a high event rate is favourable. The available-case, best-case and worst-case analyses showed identical results, including the GRADE assessment.
Quality of life	No studies evaluated this outcome					
Adverse effects other than cardiac damage						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No cardioprotective intervention	Dexrazoxane				
Secondary malignant neoplasms Available-case analysis Follow-up ranged between 0.01 and 15 years (nm for 1 study)	10 per 1000[a]	31 per 1000 (11 to 83)	RR 3.08 (1.13 to 8.38)	1015 (3 studies)	⊕⊕⊖⊖ **Low**[c,l]	The available-case and worst-case analyses were identical; the best-case analysis showed the same direction of effect, but the result was not different between treatment groups (RR 2.51 (0.96 to 6.53). GRADE assessments were comparable for all analyses.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

Footnotes

CI: confidence interval, CTCAEv2: Common Terminology Criteria for Adverse Events, version 2, e.g.: for example, HR: hazard ratio, LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, MUGA: multigated acquisition scan, NCI: National Cancer institute, nm: not mentioned, P: P value, RR: risk ratio

[a] The assumed risk is based on the overall prevalence in the control group(s) of the included study/ies.

[b] Unclear risk of selection and detection bias in 2 (67%) studies, high risk of performance bias in all studies, high risk of attrition bias and selective reporting in 1 (33%) study, unclear risk of other bias in all studies (downgraded 1 level).

[c] As these were relatively small studies with a total number of events fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook), we downgraded one level.

[d] Unclear risk of selection and other bias in all studies, high risk of performance bias in all studies (downgraded 1 level).

[e] Unclear risk of selection, detection and other bias, and high risk of performance and attrition bias (downgraded 2 levels).

[f] We did not downgrade for imprecision; it was a small study but the effect was large, the 95% CI is small and below no effect.

[g] Unclear risk of selection, detection and other bias, high risk of performance and attrition bias (downgraded 2 levels).

[h] As this was a small study with a total number of events fewer than 300 (the threshold rule-of-thumb value stated in the GRADEpro handbook (GRADEpro handbook), we downgraded 1 level.

[i] The assumed risk is based on the number of participants who died in the control groups of the included studies.

[j] Unclear risk of attrition and other bias, high risk of performance bias and selective reporting (downgraded 2 levels).

[k] Unclear risk of selection, detection and other bias; high risk of performance bias (downgraded 1 level).

[l] Unclear risk of selection, detection and other bias in all studies; high risk of performance bias in all studies (downgraded 1 level).

Clinical heart failure

Adults

We could extract data on clinical heart failure from seven studies with a total of 1249 participants (Lopez 1998; Marty 2006; Speyer 1992; Sun 2016; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996). The available-case analysis (1221 participants) showed a benefit in favour of dexrazoxane treatment (RR 0.22, 95% CI 0.11 to 0.43; P < 0.001; moderate-quality evidence; Analysis 1.1; Summary of findings 1; Figure 3); there were 11 cases among the 596 available participants in the dexrazoxane group and 67 cases among the 625 control participants. The relative effect of Sun 2016 was not estimable for the meta-analysis since none of the participants developed clinical heart failure. Intention-to-treat (ITT) analyses (1249 participants) showed a comparable difference between the treatment groups: the RR for the best-case scenario (i.e. 11 cases among 612 participants in the dexrazoxane group and 79 cases among 637 participants in the control group) was 0.22 (95% CI 0.11 to 0.43; P < 0.001; moderate-quality evidence; Analysis 1.2). The RR for the worst-case scenario (i.e. 27 cases among 612 participants in the dexrazoxane group and 79 cases among 637 participants in the control group) was 0.42 (95% CI 0.21 to 0.84; P = 0.01; moderate-quality evidence; Analysis 1.3). Unexplained significant heterogeneity (I^2 = 52%) appeared in this analysis.

Children

We could extract data on clinical heart failure from three studies with a total of 885 participants (DFCI 95-01; P9404; P9425). The available-case analysis of clinical heart failure showed no difference between the treatment groups (RR 0.20, 95% CI 0.01 to 4.19; P = 0.30; low-quality evidence; Analysis 1.1; Summary of findings 2; Figure 3). There were zero cases among the 447 available participants in the dexrazoxane group and two cases among the 438 available control participants. The relative effects of DFCI 95-01 and P9404 were not estimable for the meta-analysis since none of the participants developed clinical heart failure. ITT analyses (959 participants) also showed no difference between the treatment groups: the RR for the best-case scenario (no cases among 485 participants in the dexrazoxane group and 2 cases among 474 control participants) was 0.20 (95% CI 0.01 to 4.19; P = 0.30; low-quality evidence; Analysis 1.2). The relative effects of DFCI 95-01 and P9404 were not estimable, again as a result of zero events in both treatment groups. The RR for the worst-case scenario (i.e. 38 cases among 485 participants in the dexrazoxane group and 38 cases among 474 participants in the control group) was 0.99

(95% CI 0.68 to 1.43; P = 0.95; low-quality evidence; Analysis 1.3). The relative effect of P9404 was not estimable as a result of zero events in both treatment groups.

We excluded the study of Wexler 1996 from this analysis since, in this study, it was not possible to separate cases of clinical heart failure and subclinical myocardial dysfunction.

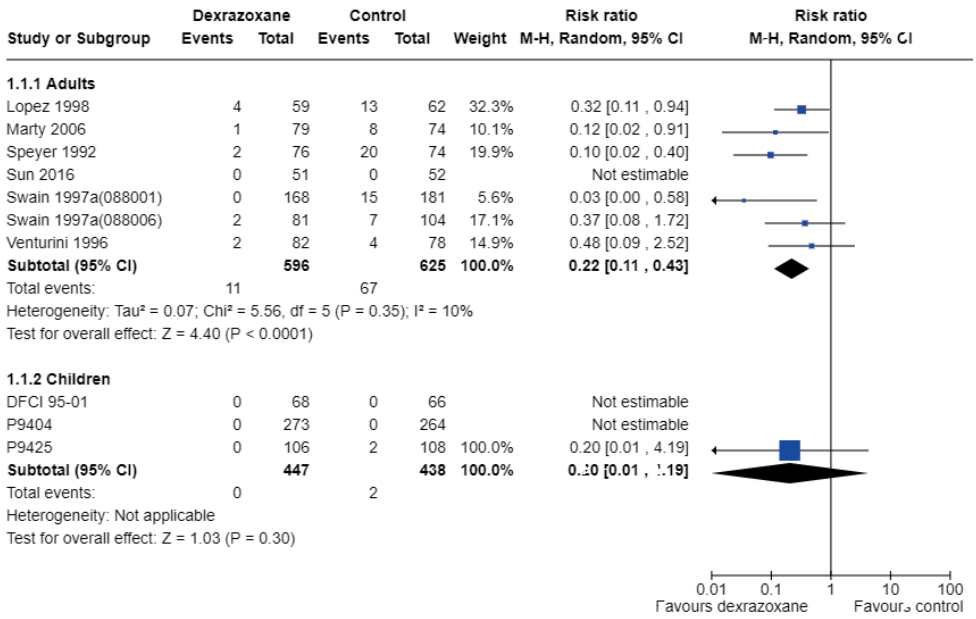

Figure 3. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.1 Clinical heart failure available-case.

Cardiomyopathy/heart failure as primary cause of death

Adults

The outcome cardiomyopathy/heart failure as primary cause of death was not assessed in any of the studies with adults.

Children

We could extract data on cardiomyopathy/heart failure as primary cause of death from three studies with a total of 1008 participants (P9404; P9425; P9426). Since all studies reported zero events in both the dexrazoxane group (507 participants) and control group (501 participants), the relative effect was not estimable in the available-case analysis (low-

quality evidence; Analysis 1.4; Summary of findings 2). ITT analyses (best-case and worst-case) showed identical results.

In these three studies, two participants (both from the control group; as results were provided only for the three studies combined (P9404; P9425; P9426), it is not known from which individual study these children came) died as a result of cardiomyopathy/heart failure listed as a secondary cause of death. No difference was identified (data not shown): RR 0.20 (95% CI 0.01 to 4.11; P = 0.29).

Heart failure (that is, clinical heart failure and subclinical myocardial dysfunction combined)

We split the analysis of heart failure (that is, clinical heart failure and subclinical myocardial dysfunction combined) into separate analyses with comparable definitions because the definitions used in the included studies were too different to pool them all together. See Characteristics of included studies for exact definitions.

Adults

Data on heart failure could be extracted from four studies using comparable definitions (Lopez 1998; Marty 2006; Speyer 1992; Venturini 1996). The available-case analysis was based on the results of Lopez 1998, Marty 2006 and Venturini 1996 with a total of 417 participants and showed a benefit for dexrazoxane treatment (RR 0.37, 95% CI 0.24 to 0.56; P < 0.001; moderate-quality evidence; Analysis 1.5; Summary of findings 1; Figure 4); there were 24 cases among the 207 available participants in the dexrazoxane group and 66 cases among the 210 control participants. ITT analyses demonstrated the same benefit of dexrazoxane. The RR for the worst-case scenario (i.e. 49 cases among 232 participants in the dexrazoxane group and 79 among 223 control participants; a total of 455 participants) was 0.60 (95% CI 0.42 to 0.86; P = 0.006; moderate-quality evidence; Analysis 1.7). For the best-case scenario the study of Speyer 1992 was added which resulted in a total of 605 participants. The RR of the best-case scenario (i.e. 30 cases among 308 participants in the dexrazoxane group and 103 among 297 control participants) was 0.29 (95% CI 0.19 to 0.44; P < 0.001; moderate-quality evidence; Analysis 1.6).

Data on heart failure could be extracted from two other studies with a total of 534 participants using another comparable definition (Swain 1997a(088001); Swain 1997a(088006)). The available-case analysis showed a benefit for dexrazoxane treatment (RR 0.46, 95% CI 0.33 to 0.66; P < 0.001; moderate-quality evidence; Analysis 1.5; Summary

of findings 1; Figure 4); there were 36 cases among the 249 available participants in the dexrazoxane group and 89 cases among the 285 control participants. ITT analyses demonstrated the same benefit of dexrazoxane: both the RR for the worst-case scenario and for the best-case scenario were identical to the available-case analysis.

We excluded the study of Galetta 2005 because it did not evaluate clinical heart failure and therefore the results included only cases of subclinical myocardial dysfunction. We excluded the study of Sun 2016 from this analysis because it addressed only clinical heart failure.

It should be noted that participants from the studies of Lopez 1998, Marty 2006, Speyer 1992, Swain 1997a(088001), Swain 1997a(088006) and Venturini 1996 who suffered from clinical heart failure were also included in the meta-analysis of clinical heart failure as mentioned above.

Children

Data on heart failure defined as (1) evidence of clinical congestive heart failure, (2) a reduction in left ventricular ejection fraction (LVEF) as measured by multigated acquisition scan (MUGA) to less than 45%, or (3) a decrease in LVEF as measured by MUGA of greater than 20 percentage points from baseline could be extracted from one study with a total of 33 participants (Wexler 1996). The available-case analysis showed a benefit for dexrazoxane treatment (RR 0.33, 95% CI 0.13 to 0.85; P = 0.02; low-quality evidence; Analysis 1.5; Summary of findings 2; Figure 4); there were 4 cases among the 18 available participants in the dexrazoxane group and 10 cases among the 15 control participants. ITT analyses showed similar results: the RR for the worst-case scenario (i.e. 6 cases among 20 participants in the dexrazoxane group and 13 among 18 participants in the control group; total of 38 participants) was 0.42 (95% CI 0.20 to 0.86; P = 0.02; low-quality evidence; Analysis 1.7), and the RR for the best-case scenario (i.e. 4 cases among 20 participants in the dexrazoxane group and 10 cases among 18 control participants; total of 38 participants) was 0.36 (95% CI 0.14 to 0.95; P = 0.04; low-quality evidence; Analysis 1.6).

Data on heart failure defined as clinical heart failure (no definition provided) or subclinical myocardial dysfunction defined as decreased left ventricular fractional shortening (LVFS) could be extracted from one study with a total of 537 participants (P9404). We were not able to calculate a RR since there was only study available in which one of the treatment groups experienced no events (zero cases among 273 participants in the dexrazoxane group and three cases among 264 participants in the control group). Therefore, we used Fischer's exact test instead (P = 0.12; very low-quality evidence). Only a best-case analysis

could be performed because it was unclear how many participants were lost to follow-up.

It should be noted that participants from the study of P9404 who suffered from clinical heart failure were also included in the meta-analysis of clinical heart failure as mentioned above.

We excluded the study of P9425 since their results only include cases of clinical heart failure. In the study of DFCI 95-01, the necessary information on the occurrence of subclinical myocardial dysfunction was not provided.

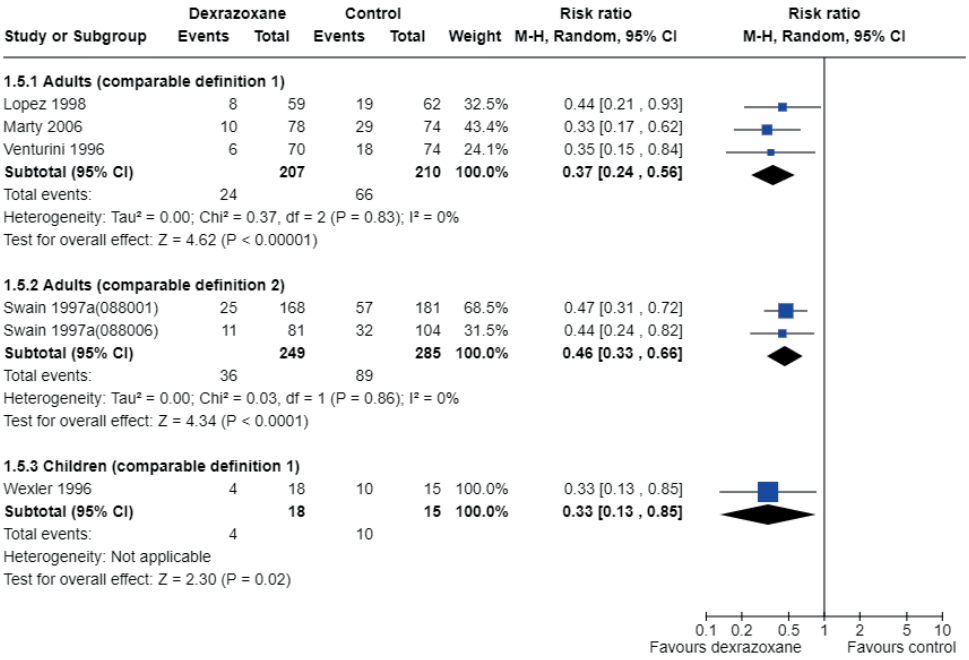

Figure 4. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.5 Heart failure (i.e. clinical and subclinical heart failure combined) available-case.

Overall survival (OS)

Adults

Data on OS could be extracted from four studies (Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)). Two studies (Swain 1997a(088001); Swain 1997a(088006)) presented HRs with 95% CIs, and the remaining two studies provided survival curves (Marty 2006; Speyer 1992).

The meta-analysis showed no difference between the treatment groups (HR 1.04, 95% CI 0.88 to 1.23, P = 0.65; moderate-quality evidence; Analysis 1.8; Summary of findings 1; Figure 5; number of participants included in the analysis unclear).

We excluded the study of Venturini 1996 from this analysis since it did not include the two participants who did not receive any chemotherapy in the evaluation of survival. We excluded the study of Lopez 1998 from this analysis since we were not able to reliably extract data needed to use Parmar's method for the assessment of survival for this study. None of the excluded studies showed differences between the treatment groups.

Median overall survival durations of the individual studies are shown in Table 1. No differences between the treatment arms were found.

Children

Data on OS could not be extracted from any of the studies in children.

We excluded the study of Wexler 1996 from this analysis since it was impossible to separate the three non-randomised participants from the randomised participants in the dexrazoxane group. However, in this study, there was no significant difference in overall survival between the treatment groups. We excluded P9404 from this analysis since we were not able to reliably extract data needed to use Parmar's method for the assessment of overall survival. In addition, more long-term follow-up data on overall mortality were available.

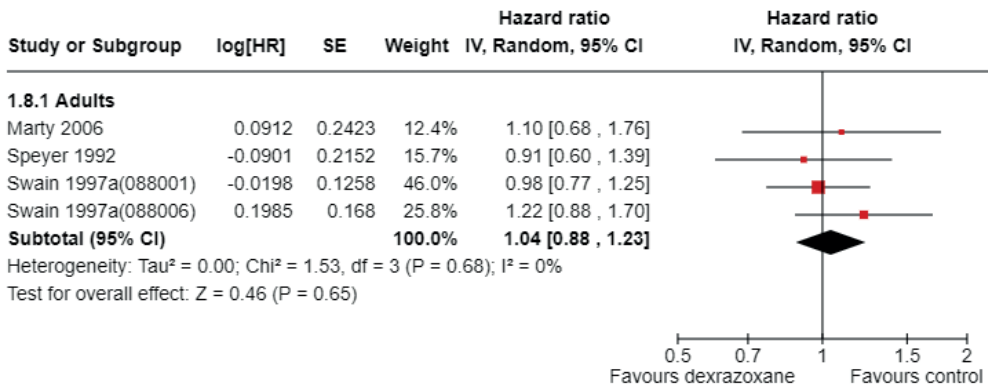

Figure 5. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.8 Overall survival.

Overall mortality

Adults

Overall mortality was not assessed in the studies in adults.

Children

Data on overall mortality could be extracted from three studies with 1008 participants in total (P9404; P9425; P9426). The included studies presented hazard rations (HRs) with 95% CIs. The meta-analysis demonstrated no difference between the treatment groups (HR 1.01, 95% CI 0.72 to 1.42, P = 0.96; low-quality evidence; Analysis 1.9; Summary of findings 2; Figure 6). Median overall survival durations for each individual study were not provided.

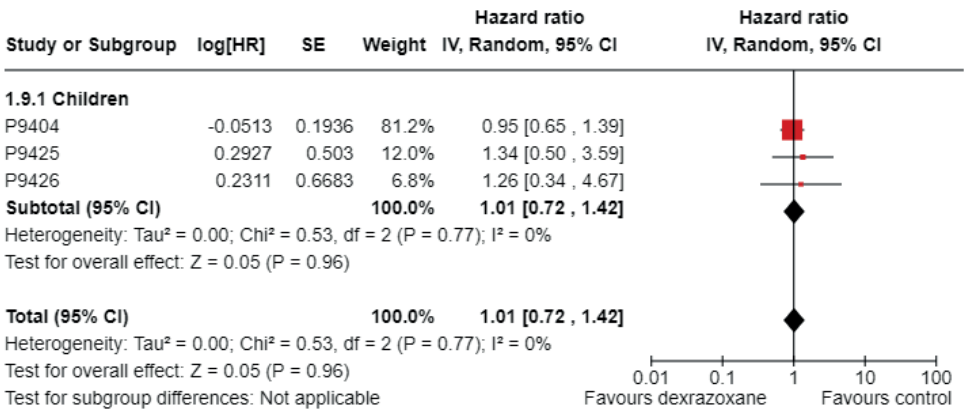

Figure 6. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.9 Overall mortality.

Progression-free survival

Adults

Data on PFS could be extracted from four studies (Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)). The Swain 1997a(088001) and Swain 1997a(088006) studies presented HRs with 95% CIs and the other two studies provided survival curves (Marty 2006; Speyer 1992).

As not all studies used comparable definitions of progression free survival, we split this analysis into three separate analyses. See Characteristics of included studies for exact definitions.

The study of Marty 2006 assessed PFS in 164 participants and defined it as time from first date of complete response, partial response or stable disease until the date progressive disease was first noticed. The analysis showed a difference in favour of dexrazoxane treatment (HR 0.62, 95% CI 0.43 to 0.90; P = 0.01; low- quality evidence; Analysis 1.10; Summary of findings 1; Figure 7).

The study of Speyer 1992 defined PFS as time to progression; however, they did not mention the starting point nor the number of participants assessed. In this analysis, there was no difference between the treatment groups (HR 0.95, 95% CI 0.64 to 1.40; P = 0.80; low-quality evidence; Analysis 1.10; Summary of findings 1; Figure 7).

The Swain 1997a(088001) and Swain 1997a(088006) studies defined PFS as time from randomisation to progression either on or off treatment. It was unclear how many participants were assessed for PFS in these studies. The analysis demonstrated no difference between the treatment groups (HR 1.18, 95% CI 0.97 to 1.43; P = 0.10; moderate-quality evidence; Analysis 1.10; Summary of findings 1; Figure 7).

We excluded the study of Venturini 1996 from this analysis since it did not include the two participants who did not receive any chemotherapy in the evaluation of survival. We excluded the study of Lopez 1998 from this analysis since we were not able to reliably extract the data needed to use Parmar's method for the assessment of survival for this study. However, none of the excluded studies showed differences between the treatment arms.

Median progression-free survival durations of the individual studies are shown in Table 1. No differences between the treatment arms were found.

Children

Data on PFS could not be extracted from any of the studies in children.

Study or Subgroup	log[HR]	SE	Weight	Hazard ratio IV, Random, 95% CI
1.10.1 Adults (PFS defined as time from first date of complete response, partial response or stable disease until the date progressive disease was first noticed)				
Marty 2006	-0.4708	0.1852	100.0%	0.62 [0.43 , 0.90]
Subtotal (95% CI)			**100.0%**	**0.62 [0.43 , 0.90]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.54 (P = 0.01)				
1.10.2 Adults (PFS defined as time to progression; starting point nm)				
Speyer 1992	-0.0508	0.1981	100.0%	0.95 [0.64 , 1.40]
Subtotal (95% CI)			**100.0%**	**0.95 [0.64 , 1.40]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.26 (P = 0.80)				
1.10.3 Adults (PFS defined as time from randomisation to progression either on or off treatment)				
Swain 1997a(088001)	0.1508	0.1227	64.7%	1.16 [0.91 , 1.48]
Swain 1997a(088006)	0.1863	0.166	35.3%	1.20 [0.87 , 1.67]
Subtotal (95% CI)			**100.0%**	**1.18 [0.97 , 1.43]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%				
Test for overall effect: Z = 1.66 (P = 0.10)				

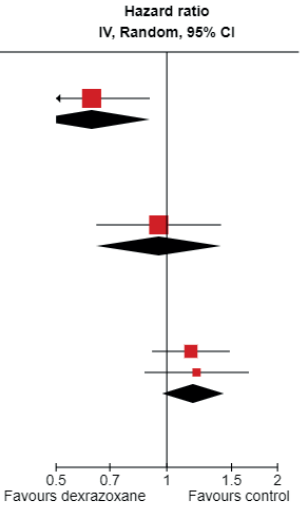

Figure 7. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.10 Progression-free survival.

Tumour response rate

Tumour response rate was defined as the number of participants in complete and partial remission for adult studies and the number of participants in complete remission for paediatric studies. Please note that due to the nature of this measurement, a high event rate is favourable. Therefore, in the figure of this analysis 'favours control' is on the left and 'favours dexrazoxane' is on the right, as opposed to the figures for the other analyses.

Adults

We could extract data on tumour response rate from six studies with a total of 956 participants (Lopez 1998; Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996). These studies used comparable criteria to assess tumour response rate. The studies Swain 1997a(088001) and Swain 1997a(088006)) included only participants with evaluable disease. The availablecase analysis demonstrated no difference between the treatment groups (RR 0.91, 95% CI 0.79 to 1.04; P = 0.16; moderate-quality evidence; Analysis 1.11; Summary of findings 1; Figure 8); there were 223 complete and partial responses among 468 participants randomised to dexrazoxane and 260 among 488 randomised to the control group. ITT analyses (1021 participants) also showed no difference between the treatment groups: the RR for the worst-case scenario (i.e. 223 cases among 503 participants in the dexrazoxane group and 260 cases among 518 participants in the control group) was 0.89 (95% CI 0.78 to 1.01; P = 0.07; moderatequality evidence; Analysis 1.13), and the RR for the best-case scenario (i.e. 258 cases among 503 participants in the dexrazoxane group and 290 cases among 518 control participants) was 0.94 (95% CI 0.82 to 1.08; P = 0.37; moderate-quality evidence; Analysis 1.12).

Children

We could extract data on tumour response rate from two studies. As no comparable definitions were used, we split this analysis into two separate analyses.

The DFCI 95-01 study did not provide a definition of complete remission and only a best-case analysis could be performed because it was unclear how many participants were lost to follow-up. It demonstrated no difference between the treatment groups (RR 1.01, 95% CI 0.95 to 1.07; P = 0.69; very low-quality evidence; Analysis 1.12; Summary of findings 2); there were 101 complete remissions among 105 participants randomised to dexrazoxane and 96 among 101 randomised to the control group.

The P9425 study defined complete response as disappearance of active Hodgkin lymphoma (gallium negative, ≥ 70% decrease in the sum of the products of the perpendicular diameters of measurable lesions, and negative bone marrow or bone scan if initially positive). The available-case analysis demonstrated no difference between the treatment groups (RR 0.92, 95% CI 0.84 to 1.01; P = 0.07; low-quality evidence; Analysis 1.11; Summary of findings 2; Figure 8); there were 87 complete responses among 101 participants randomised to dexrazoxane and 93 among 99 randomised to the control group. ITT analyses also showed no difference between the treatment groups: the RR for the worst-case scenario (i.e. 87 cases among 107 participants in the dexrazoxane group and 93 cases among 109 participants in the control group) was 0.95 (95% CI 0.85 to 1.07 to 1.01, P = 0.43; low-quality evidence; Analysis 1.13), and the RR for the best-case scenario (i.e. 93 cases among 107 participants in the dexrazoxane group and 103 cases among 109 control participants) was 0.92 (95% CI 0.84 to 1.00; P = 0.06; lowquality evidence; Analysis 1.12).

We excluded the study of Wexler 1996 from this analysis since it was impossible to separate the three non-randomised participants from the randomised participants in the dexrazoxane group.

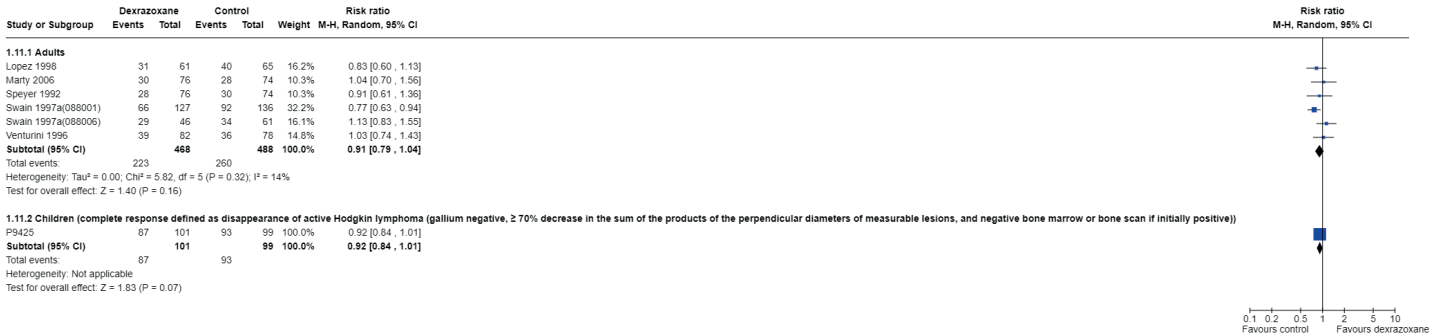

Figure 8. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.11 Response rate available-case.

Quality of life (QoL)

None of the studies evaluated QoL.

Adverse effects

Since all participants receiving chemotherapy will suffer from side effects, we decided to analyse only the severe and life-threatening effects. For studies using the Eastern Cooperative Oncology Group (ECOG) (Oken 1982), World Health Organization (WHO) (Miller 1981), or National Cancer Institute (NCI) Common Toxicity Criteria (CTC), currently known as Common Terminology Criteria for Adverse Events (CTCAE) (for different versions, see: ctep.cancer.gov/protocoldevelopment/ electronic_applications/ctc.htm), we defined this as grade 3 (severe) or grade 4 (life-threatening); for the study of Speyer 1992 we excluded the two lowest grades reported. For studies that did not provide definitions we used severe cases (Sun 2016), or all cases (P9426). Secondary malignant neoplasm (SMN) was considered as a severe side effect irrespective of the availability of an exact definition. We classified the adverse effects based on the (organ) system involved. It was possible to perform meta-analyses for adverse effects for which more than one RCT was available. For adverse effects for which only one RCT was available, we provide descriptive results (all RRs, 95% CIs and P values mentioned below are calculated in Review Manager 5 with the random-effects model, unless stated otherwise). The timing and frequency of the evaluation of the side effects in the different studies was not clear. Not all studies addressed all adverse effects. For results not included as a figure, see Analysis 1.14, Analysis 1.15, Analysis 1.16, Analysis 1.17, Analysis 1.18, Analysis 1.19, Analysis 1.20, Analysis 1.21, Analysis 1.22, Analysis 1.23 and Analysis 1.24 for more detailed information.

Adults

Data on adverse effects could be extracted from seven studies: Lopez 1998 and Venturini 1996 used the WHO criteria; Swain 1997a(088001) and Swain 1997a(088006) used the ECOG criteria, and Marty 2006 used the CTC (version 2). The study of Speyer 1992 provided definitions of the different adverse effects used in the study without a reference. Sun 2016 did not provide definitions.

Children

Data on adverse effects could be extracted from four RCTs: P9404 and P9425 used the CTCAEv2.0. For the studies of DFCI 95-01 and P9426, no definitions were provided. We excluded the study of Wexler 1996 from this analysis since this study did not report the number of participants having suffered an adverse effect.

Secondary malignant neoplasm (SMN)

Adults

SMN was not assessed in the studies with adults.

Children

Data could be extracted from four studies (DFCI 95-01; P9404; P9425; P9426). The available-case analysis was based on the results of P9404, P9425 and P9426 with a total of 1015 participants and showed a difference in favour of the control group (RR 3.08, 95% CI 1.13 to 8.38; P = 0.03; low-quality evidence; Analysis 1.14; Summary of findings 2; Figure 9). There were 16 cases of SMN among the 512 available participants in the dexrazoxane group and 5 cases among the 503 control participants. ITT analyses demonstrated the following results: the results for the worst-case scenario were identical to the available-case analysis. For the best-case scenario, the study of DFCI 95-01 could be added which resulted in a total of 1220 participants. The results of the best-case scenario (i.e. 16 cases among 617 participants in the dexrazoxane group and 6 cases among the 607 participants in the control group) showed the same direction of effect, but now the result was not different between the treatment groups (RR 2.51, 95% CI 0.96 to 6.53; P = 0.06; low-quality evidence).

In the dexrazoxane group, there were seven cases with acute myeloid leukaemia (AML), five cases with brain tumours, two cases with papillary carcinoma, one case with osteosarcoma and one case with myelodysplastic syndrome. In the control group, there were three cases with AML, one case with myeloid sarcoma, one case with lymphoma and one case with melanoma (see Table 2 for more information).

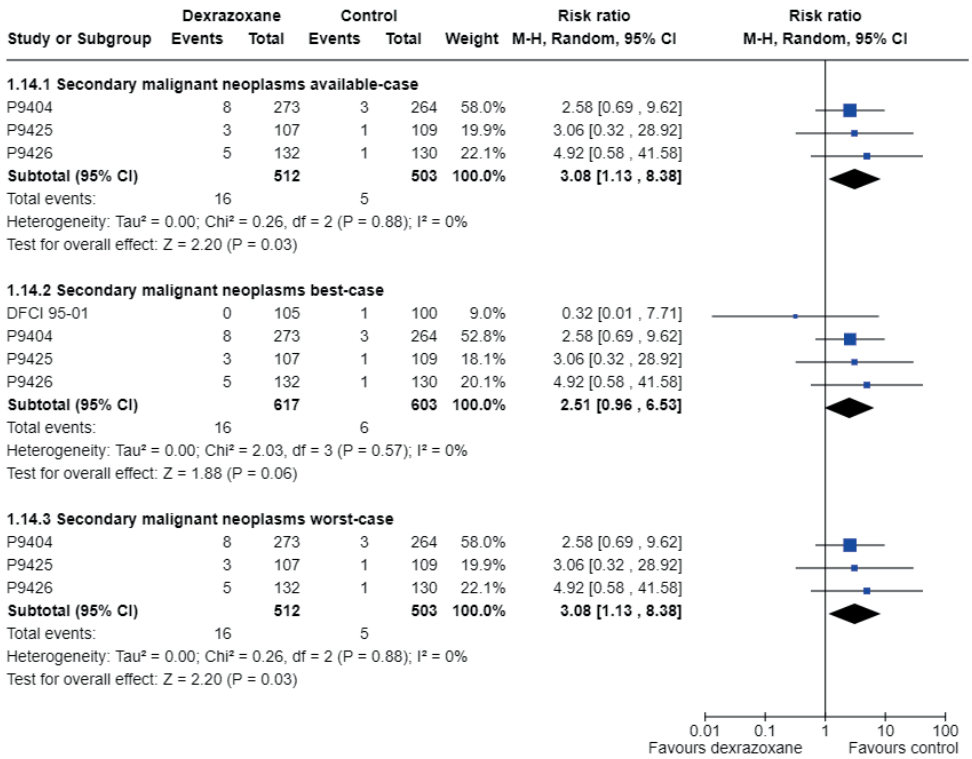

Figure 9. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane or placebo, outcome: 1.14 Adverse effects: Secondary malignant neoplasms (Children).

Haematological effects

Adults

Thrombocytopenia

Data on thrombocytopenia (defined as grade 3 or 4 according to WHO or the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 2 (CTCAEv2) criteria, which were comparable) could be extracted from three studies with a total of 452 participants (Lopez 1998; Marty 2006; Venturini 1996). The available-case analysis showed no difference between the treatment groups (RR 1.03, 95% CI 0.48 to 2.20; P = 0.94). There were 11 cases among the 229 available participants in the dexrazoxane group and 11 cases among the 223 participants in the control group. The relative effects of Venturini 1996 were not estimablefor the meta-analysis since none of the participants developed thrombocytopenia. ITT analyses demonstrated comparable results (455 participants). For more details, see Analysis 1.15.

Neutropenia

Data on neutropenia (defined as grade 3 or 4 according to WHO or CTCAEv2 criteria, which were comparable) could be extracted from two studies with a total of 292 participants (Lopez 1998; Marty 2006). The available-case analysis showed no difference between the treatment groups (RR 1.05, 95% CI 0.96 to 1.15; P = 0.32). There were 91 cases among the 147 available participants in the dexrazoxane group and 88 cases among the 145 participants in the control group. ITT analyses demonstrated comparable results (293 participants). For more details, see Analysis 1.15.

Abnormal granulocyte count at nadir

Data on abnormal granulocyte count at nadir (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 221 cases among the 249 participants in the dexrazoxane group and 244 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 1.04, 95% CI 0.96 to 1.13; P = 0.29). For more details, see Analysis 1.15.

Abnormal granulocyte count at recovery

Data on abnormal granulocyte count at recovery (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 42 cases among the 249 participants in the dexrazoxane group and 57 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.85, 95% CI 0.59 to 1.21; P = 0.36). For more details, see Analysis 1.15.

Abnormal white blood cell count at nadir

Data on abnormal white blood cell count at nadir (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies with a total of 534 participants (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (195 cases among the 249 participants in the dexrazoxane group and 193 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed a difference in favour of the control treatment (RR 1.16, 95% CI 1.05 to 1.29; P = 0.004). For more details, see Analysis 1.15.

Abnormal white blood cell count at recovery

Data on abnormal white blood cell count at recovery (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 14 cases among the 249 participants in the dexrazoxane group and 23 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.69, 95% CI 0.36 to 1.31; P = 0.26). For more details, see Analysis 1.15.

Abnormal platelet count at nadir

Data on abnormal platelet count at nadir (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 21 cases among the 249 participants in the dexrazoxane group and 26 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.88, 95% CI 0.42 to 1.84; P = 0.73). For more details, see Analysis 1.15.

Abnormal platelet count at recovery

Data on abnormal platelet count at recovery (defined as grade 3 or 4 according to ECOG criteria) could be extracted from two studies (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. two cases among the 249 participants in the dexrazoxane group and 3 cases among the 285 in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.84, 95% CI 0.16 to 4.42; P = 0.83). For more details, see data and Analysis 1.15.

Anaemia

Data on anaemia (defined as grade 3 or 4 according to WHO or CTCAEv2 criteria, which were comparable) could be extracted from three studies with a total of 452 participants (Lopez 1998; Marty 2006; Venturini 1996). The available-case analysis showed no difference between the treatment groups (RR 1.37, 95% CI 0.79 to 2.39; P = 0.26). There were 27 cases among the 229 available participants in the dexrazoxane group and 19 cases among the 223 participants in the control group. ITT analyses demonstrated comparable results (455 participants). For more details, see Analysis 1.15.

Myelosuppression

Data on severe myelosuppression (definition not provided) could be extracted from one study with a total of 108 participants (Sun 2016). The available-case analysis showed no difference between the treatment groups (RR 2.00, 95% CI 0.19 to 21.41; P = 0.57). There were two cases among the 54 available participants in the dexrazoxane group and one among the 54 participants in the control group. ITT analyses demonstrated comparable results (110 participants). For more details, see Analysis 1.15.

Leukopenia

Data on leukopenia (defined as grade 3 or 4 according to WHO or CTCAEv2 criteria, which were comparable) could be extracted from two studies with a total of 324 participants (Marty 2006; Venturini 1996). The available-case analysis showed no difference between the treatment groups (RR 1.10, 95% CI 0.66 to 1.83; P = 0.71). There were 27 cases among the 167 available participants in the dexrazoxane group and 23 cases among the 157 participants in the control group. ITT analyses demonstrated comparable results (326 participants). For more details, see Analysis 1.15.

Children

Lymphocytes

Data on lymphocytes (no definition provided) could be extracted from one study with a total of 222 participants (P9426). The available-case analysis showed no difference between the treatment groups (RR 1.04, 95% CI 0.07 to 16.37; P = 0.98). There was one case among the 109 available participants in the dexrazoxane group and one case among the 113 participants in the control group. ITT analyses demonstrated comparable results (225 participants). For more details, see Analysis 1.16.

Haemoglobin

Data on haemoglobin could be extracted from two studies (P9425; P9426); however, we analysed the studies separately because P9426 did not provide a definition for haemoglobin. P9425 used grade 3 or 4 according to the CTCAEv2 criteria. In both studies, the available-case analysis demonstrated a difference in favour of the control group: for P9426, the RR was 2.96 (95% CI 1.31 to 6.72; P = 0.009), there were 20 cases among the 109 available participants in the dexrazoxane group and 7 cases among the 113 participants in the control group (222 participants in total); for P9425, the RR was 1.48

(95% CI 1.13 to 1.95; P = 0.005), there were 64 cases among the 106 available participants in the dexrazoxane group and 44 cases among the 108 participants in the control group (214 participants in total). ITT analyses demonstrated comparable results for both P9426 (255 participants) and P9425 (216 participants). For more details, see Analysis 1.16.

White blood cell count

Data on white blood cell count (no definition provided) could be extracted from one study with a total of 222 participants (P9426). The available-case analysis showed a difference in favour of the control group (RR 1.87, 95% CI 1.30 to 2.68; P < 0.001). There were 54 cases among the 109 available participants in the dexrazoxane group and 30 cases among the 113 participants in the control group. ITT analyses demonstrated comparable results (255 participants). For more details, see Analysis 1.16.

Thrombosis

Data on thrombosis (defined as grade 3 or 4 according to NCI CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-case analysis demonstrated no difference between the treatment groups (RR 4.08, 95% CI 0.46 to 35.87; P = 0.21). There were four cases among the 106 available participants in the dexrazoxane group and one case among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.16.

Platelets

Data on platelets could be extracted from two studies (P9425; P9426); however, we analysed the studies separately because P9426 did not provide a definition for platelets. P9425 used grade 3 or 4 according to the NCI CTCAEv2 criteria. In the study of P9426, the available-case analysis demonstrated no difference between the treatment groups (RR 1.87, 95% CI 0.90 to 3.86; P = 0.09). There were 18 cases among the 109 available participants in the dexrazoxane group and 10 cases among the 113 participants in the control group (222 participants in total). ITT analyses demonstrated comparable results (255 participants). For more details, see Analysis 1.16.

In the study of P9425, the available-case analysis demonstrated a difference in favour of the control group (RR 2.45, 95% CI 1.79 to 3.35; P < 0.001). There were 77 cases among the 106 available participants in the dexrazoxane group and 33 cases among the 108 participants in

the control group (214 participants in total). ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.16.

Absolute neutrophil count

Data on absolute neutrophil count could be extracted from two studies (P9425; P9426); however, we analysed the studies separately because P9426 did not provide a definition for absolute neutrophil count grade 3 or 4. P9425 used grade 3 or 4 according to CTCAEv2 criteria. In the study of P9426, the available-case analysis demonstrated a difference in favour of the control group (RR 1.27, 95% CI 1.03 to 1.58; P = 0.02). There were 75 cases among the 109 available participants in the dexrazoxane group and 61 cases among the 113 participants in the control group (222 participants in total). ITT analyses (255 participants) demonstrated comparable results regarding the worst-case scenario with a RR of 1.23 (95% CI 1.03 to 1.47; P = 0.02), but for the best-case scenario there was no difference between the treatment groups with a RR of 1.24 (95% CI 0.98 to 1.56; P = 0.07).

In the study of P9425, the available-case analysis demonstrated a difference in favour of the control group (RR 1.10, 95% CI 1.00 to 1.20; P = 0.04). There were 100 cases among the 106 available participants in the dexrazoxane group and 93 cases among the 108 participants in the control group (214 participants in total). ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.16.

Haematological effects

Data on haematological effects (defined as grade 3 or 4 according to CTCAEv2 criteria) could be extracted from one study with a total of 537 participants (P9404). The available-case analysis showed no difference between the treatment groups (RR 0.99, 95% CI 0.94 to 1.05; P = 0.77). There were 243 cases among the 273 available participants in the dexrazoxane group and 237 cases among the 264 participants in the control group. ITT analyses demonstrated identical results since there were no missing data in this study.

Immune system/infectious effects

Adults

Fever

Data on fever could be extracted from three studies (Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we performed two separate analyses as the

definitions used were not comparable. Data on fever (grade 3 or 4 according to ECOG criteria) could be extracted from two trials (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 25 cases among the 249 participants in the dexrazoxane group and 20 cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 1.43, 95% CI 0.81 to 2.54; P = 0.22).

Data on fever (defined as grade 3 or 4 according to the WHO criteria) could be extracted from one study (Venturini 1996). There was one case among the 82 available participants in the dexrazoxane group and zero cases among the 78 participants in the control group. We were not able to calculate a RR since there was only one study available and one of its treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 1.00). Best-case and worst-case scenarios showed identical results (162 participants). For more details and data, see Table 3.

Febrile bone marrow aplasia

Data on febrile bone marrow aplasia (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). The availablecase analysis showed no difference between the treatment groups (RR 3.72, 95% CI 0.42 to 32.55; P = 0.24). There were four cases among the 85 available participants in the dexrazoxane group and one case among the 79 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Febrile neutropenia

Data on febrile neutropenia (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). The available-case analysis showed no difference between the treatment groups (RR 1.27, 95% CI 0.62 to 2.59; P = 0.52). There were 15 cases among the 85 available participants in the dexrazoxane group and 11 cases among 79 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Fever with positive blood cultures

Data on fever with positive blood cultures (no reference provided) could be extracted from one study with a total of 150 participants (Speyer 1992). The available-case analysis showed no difference between the treatment groups (RR 0.65, 95% CI 0.11 to 3.77; P =

0.63). There were two cases among the 76 available participants in the dexrazoxane group and three cases among 74 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Fever with other positive cultures

Data on fever with other positive cultures (no reference provided) could be extracted from one study with a total of 150 participants (Speyer 1992). The available-case analysis showed no difference between the treatment groups (RR 1.95, 95% CI 0.37 to 10.31; P = 0.43). There were four cases among the 76 available participants in the dexrazoxane group and two cases among the 74 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Pyrexia

Data on pyrexia (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). There were two cases among the 85 available participants in the dexrazoxane group and zero cases among the 79 participants in the control group. We were not able to calculate a RR since there was only study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 0.50). Best-case and worstcase scenarios showed identical results. For more details and data, see Table 3.

Children

Sepsis

Data on sepsis could be extracted from two studies (P9425; P9426); however, we analysed the studies separately as P9426 reported only that the sepsis was caused by bacteria and provided no further information. P9425 used grade 3 or 4 according to the CTCAEv2 criteria. In both studies, the available-case analysis demonstrated no difference between the treatment groups: for P9426, the RR was 1.04 (95% CI 0.07 to 16.37; P = 0.98), there was one case among the 109 available participants in the dexrazoxane group and one case among the 113 participants in the control group (222 participants in total); for P9425, the RR was 2.04 (95% CI 0.96 to 4.33; P = 0.06), there were 18 cases among the 106 available participants in the dexrazoxane group and 9 cases among the 108 participants in the control group (214 participants in total). ITT analyses demonstrated comparable results for both P9426 (255 participants) and P9425 (216 participants). For more details, see Analysis 1.18.

Infection

Data on infection could be extracted from three studies (P9404; P9425; P9426); however, we analysed the results of P9426 separately because it did not provide the definition it used. P9404 and P9425 used grade 3 or 4 according to the CTCAEv2 criteria; for P9425, in addition to stating that the criteria were used, for this outcome the authors also explicitly stated "not otherwise specified/unknown". In both analyses, the availablecase analysis demonstrated no difference between the treatment groups; for P9426, the RR was 0.35 (95% CI 0.04 to 3.27; P = 0.35), there was one case among the 109 available participants in the dexrazoxane group and 13 cases among the 113 participants in the control group (222 participants in total); for the meta-analysis of P9404 and P9425, the RR was 1.24 (95% CI 0.78 to 1.97; P = 0.35), there were 248 cases among the 379 available participants in the dexrazoxane group and 216 cases among the 372 participants in the control group (751 participants in total). Unexplained substantial heterogeneity was detected (I^2 = 91%). ITT analyses demonstrated comparable results for both P9426 (255 participants) and the metaanalysis of P9404 and P9425 (753 participants). For more details, see Analysis 1.18.

Allergic reaction

Data on allergic reaction could be extracted from two studies (P9425; P9426); however, we analysed the studies separately because P9426 did not provide a definition for allergic reaction. P9425 used grade 3 or 4 according to the CTCAEv2 criteria. In both studies, the available-case analysis demonstrated no difference between the treatment groups: for P9426, the RR was 0.26 (95% CI 0.03 to 2.28; P = 0.22), there was one case among the 109 available participants in the dexrazoxane group and four cases among the 113 participants in the control group (222 participants in total); for P9425, the RR was 3.57 (95% CI 0.76 to 16.78; P = 0.11), there were seven cases among the 106 available participants in the dexrazoxane group and two cases among the 108 participants in the control group (214 participants in total). ITT analyses demonstrated comparable results for both P9426 (255 participants) and P9425 (216 participants). For more details, see Analysis 1.18.

Gastrointestinal effects

Adults

Nausea

Data on nausea could be extracted from four studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we performed two separate analyses

as the definitions used were not comparable. Data on nausea (defined as grade 3 or 4 according to the CTCAEv2 or ECOG criteria, which were comparable) could be extracted from three studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006)). The available-case analysis was based on the results of Marty 2006 with a total of 164 participants and showed no difference between the treatment groups (RR 0.19, 95% CI 0.02 to 1.56; P = 0.12). There was one case among the 85 available participants in the dexrazoxane group and five cases among the 79 participants in the control group. ITT analyses demonstrated the following results: the RR for the worst-case scenario was identical since there were no missing data in the study of Marty 2006. For the best-case scenario, the studies Swain 1997a(088001) and Swain 1997a(088006) were added, which resulted in a total of 698 participants. The best-case scenario (i.e. 46 cases among 334 participants in the dexrazoxane group and 77 cases among 364 participants in the control group) demonstrated a benefit for dexrazoxane treatment (0.70, 95% CI 0.50 to 0.97; P = 0.03). The studies Swain 1997a(088001) and Swain 1997a(088006) could only be added to the best-case scenario as the number of missing participants was unclear.

Data on nausea (defined as grade 3 or 4 according to the WHO criteria) could be extracted from one study (Venturini 1996). The available-case analysis showed no differences between treatment groups (RR 0.95, 95% CI 0.25 to 3.67; P = 0.94; 160 participants).

There were four cases among the 82 available participants in the dexrazoxane group and four cases among the 78 participants in the control group. Best-case and worst-case scenarios showed comparable results (162 participants).

Vomiting

Data on vomiting could be extracted from four studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we performed two separate analyses as the definitions used were not comparable. Data on vomiting (defined as grade 3 or 4 according to the CTCAEv2 or ECOG criteria, which were comparable) could be extracted from three studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006)). The available-case analysis was based on the results of Marty 2006 with a total of 164 participants and showed no difference between the treatment groups (RR 0.15, 95% CI 0.02 to 1.26; P = 0.08). There was one case among the 85 available participants in the dexrazoxane group and six cases among the 79 participants in the control group. ITT analyses also demonstrated no difference between the treatment groups. The RR for the worst-case scenario was identical since there were no missing data in the study

of Marty 2006. For the best-case scenario, the studies Swain 1997a(088001) and Swain 1997a(088006) were added which resulted in a total of 698 participants. The RR for the best-case scenario (i.e. 42 cases among 334 participants in the dexrazoxane group and 60 cases among the 364 participants in the control group) was 0.71 (95% CI 0.37 to 1.39; P = 0.32). The studies Swain 1997a(088001) and Swain 1997a(088006) could only be added to the best-case scenario as the number of missing participants was unclear.

Data on vomiting (defined as grade 3 or 4 according to the WHO criteria) could be extracted from one study (Venturini 1996). The available-case analysis showed no differences between treatment groups (RR 1.11, 95% CI 0.39 to 3.16; P = 0.85; 160 participants). There were seven cases among the 82 available participants in the dexrazoxane group and six cases among the 78 participants in the control group. Best-case and worst-case scenarios showed comparable results (162 participants).

Nausea and vomiting

Data on nausea and vomiting could be extracted from two studies (Lopez 1998; Speyer 1992); however, we analysed the studies separately since the definitions differed. In the study of Lopez 1998, the available-case analysis demonstrated no difference between the treatment groups in nausea and vomiting grade 3 or 4 according to WHO criteria (RR 0.32, 95% CI 0.09 to 1.11; P = 0.07). There were 3 cases among the 62 available participants in the dexrazoxane group and 10 cases among the 66 participants in the control group (128 participants in total). ITT analyses demonstrated comparable results (129 participants). For more details, see Analysis 1.19.

The study of Speyer 1992 divided the results on nausea and vomiting into “controllable” and “intractable”. The available-case analysis on controllable nausea and vomiting demonstrated no difference between the treatment groups (RR 1.07, 95% CI 0.81 to 1.40; P = 0.46). There were 46 cases among 76 available participants in the dexrazoxane group and 42 among 74 in the control group (150 participants in total). The available-case analysis on intractable nausea and vomiting also demonstrated no difference between the treatment groups (RR 0.39, 95% CI 0.08 to 1.95; P = 0.25). There were two cases among the 76 available participants in the dexrazoxane group and five among 74 in the control group (150 participants in total). ITT analyses demonstrated identical results for both definitions since there were no missing data.

Stomatitis

Data on stomatitis could be extracted from six studies (Lopez 1998; Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we subdivided the analysis into four groups since the studies used different definitions (see Characteristics of included studies).

First, the studies of Lopez 1998 and Venturini 1996 used the same definition. The available-case analysis demonstrated no difference between the treatment groups (RR 0.96, 95% CI 0.38 to 2.44; P = 0.94). There were 13 cases among the 144 available participants in the dexrazoxane group and 14 cases among the 144 participants in the control group (288 participants in total). ITT analyses demonstrated comparable results (291 participants).

The study of Speyer 1992 was also analysed separately. This study divided the results on stomatitis into "ulcers can eat" and "ulcers cannot eat". The available-case analysis on ulcers can eat demonstrated no difference between the treatment groups (RR 0.89, 95% CI 0.40 to 1.96; P = 0.76). There were 10 cases among the 76 available participants in the dexrazoxane group and 11 cases among the 74 participants in the control group (150 participants in total). The available-case analysis on ulcers cannot eat also demonstrated no difference between the treatment groups (RR 0.42, 95% CI 0.11 to 1.55; P = 0.25). There were three cases among the 76 available participants in the dexrazoxane group and seven cases among the 74 participants in the control group (150 participants in total). ITT analyses demonstrated identical results for both definitions since there were no missing data.

Lastly, the studies of Marty 2006, Swain 1997a(088001) and Swain 1997a(088006) used comparable definitions. The available-case analysis was based on the results of Marty 2006 with a total of 164 participants and showed no difference between the treatment groups (RR 0.19, 95% CI 0.02 to 1.56; P = 0.12). There was one case among the 85 available participants in the dexrazoxane group and five cases among the 79 participants in the control group. ITT analyses demonstrated the following results: the RR for the worst-case scenario was identical since there were no missing data in the study of Marty 2006. For the best-case scenario, the studies Swain 1997a(088001) and Swain 1997a(088006) were added which resulted in a total of 698 participants. The bestcase scenario (i.e. 15 cases among 334 participants in the dexrazoxane group and 25 cases among the 364 participants in the control group) demonstrated no difference between the treatment groups (0.70, 95% CI 0.38 to 1.30; P = 0.26). The studies Swain 1997a(088001) and Swain 1997a(088006) could only be added to the best-case scenario as the number of missing participants was unclear.

In summary, all the analyses on stomatitis demonstrated no difference between the treatment groups. For more details, see Analysis 1.19.

Diarrhoea

Data on diarrhoea could be extracted from four studies (Marty 2006; Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we subdivided the analysis into three groups since the studies used different definitions.

First, the study of Marty 2006 was analysed separately. Diarrhoea was defined as grade 3 or 4 according to the CTCAEv2 criteria. The available-case analysis showed no difference between the treatment groups (RR 0.93, 95% CI 0.06 to 14.61; P = 0.96). There was one case among the 85 available participants in the dexrazoxane group and one among 79 in the control group (164 participants in total). ITT analyses demonstrated identical results since there were no missing data.

Second, the studies of Swain 1997a(088001) and Swain 1997a(088006) used the same definition. Diarrhoea was defined as grade 3 or 4 according to the ECOG criteria. Only the bestcase scenario (i.e. 10 cases among the 249 participants in the dexrazoxane group and 10 cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 1.15, 95% CI 0.40 to 3.30; P = 0.79).

For more details, see Analysis 1.19.

Third, the study of Venturini 1996 was analysed separately. Diarrhoea was defined as grade 3 or 4 according to the WHO criteria. There were no cases in both treatment groups (82 available participants in the dexrazoxane group and 78 available participants in the control group; 160 participants in total). We were not able to calculate a RR since there was only one study available and both treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 1.00). Best-case and worst-case scenarios showed identical results (162 participants). For more details and data, see Table 3.

Constipation

Data on constipation (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). There was one case among the 85 available participants in the dexrazoxane group and zero cases among the 79 participants in the control group. We were not able to calculate a RR since

there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 1.0). The best-cases and worstcase scenarios showed identical results. For more data and details, see Table 3.

Mucosal inflammation

Data on mucosal inflammation (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). There were zero cases among the 85 available participants in the dexrazoxane group and one case among the 79 participants in the control group. We were not able to calculate a RR since there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 0.48). The best-cases and worstcase scenarios showed identical results. For more data and details, see Table 3.

Children

Nausea

Data on nausea (no definition provided) could be extracted from one study with a total of 222 participants (P9426). The availablecase analysis showed no difference between the treatment groups (RR 1.04, 95% CI 0.15 to 7.23; P = 0.97). There were two cases among the 109 available participants in the dexrazoxane group and two cases among the 113 participants in the control group. ITT analyses demonstrated comparable results (255 participants). For more details, see Analysis 1.20.

Vomiting

Data on vomiting (no definition provided) could be extracted from one study with a total of 222 participants (P9426). The availablecase analysis showed no difference between the treatment groups (RR 0.62, 95% CI 0.15 to 2.54; P = 0.51). There were three cases among the 109 available participants in the dexrazoxane group and five cases among the 113 participants in the control group. ITT analyses demonstrated comparable results (255 participants). For more details, see Analysis 1.20.

Nausea or vomiting

Data on nausea or vomiting (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-

case analysis demonstrated no difference between the treatment groups (RR 1.02, 95% CI 0.44 to 2.35; P = 0.96). There were 10 cases among the 106 available participants in the dexrazoxane group and 10 cases among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.20.

Stomatitis

Data on stomatitis (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-case analysis demonstrated no difference between the treatment groups (RR 0.99, 95% CI 0.64 to 1.51; P = 0.95). There were 30 cases among the 106 available participants in the dexrazoxane group and 31 cases among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.20.

Mucositis

Data on mucositis (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 537 participants (P9404). The available-case analysis showed a benefit for dexrazoxane treatment (RR 0.61, 95% CI 0.41 to 0.92; P = 0.02). There were 33 cases among the 273 available participants in the dexrazoxane group and 52 cases among the 264 participants in the control group. ITT analyses demonstrated identical results since there were no missing data in this study.

Typhlitis

Data on typhlitis (defined as grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-case analysis demonstrated no difference between the treatment groups (RR 3.06, 95% CI 0.85 to 10.98; P = 0.09). There were nine cases among the 106 available participants in the dexrazoxane group and three cases among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.20.

Neurological effects

Adults

Neurotoxicity

Data on neurotoxicity (grade 3 or 4 according to the ECOG criteria) could be extracted from two trials (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. two cases among the 249 participants in the dexrazoxane group and five cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.62, 95% CI 0.03 to 13.45; P = 0.76). However, unexplained heterogeneity was detected (I^2 = 63%). For more details, see Analysis 1.21.

Children

Central nervous system

Data on central nervous system grade 3 or 4 toxicity (according to the CTCAEv2 criteria) could be extracted from two studies with a total of 751 participants (P9404; P9425). P9425 explicitly stated that central nervous system included mood, cortical and cerebellar. The available-case analysis demonstrated no difference between the treatment groups (RR 1.21, 95% CI 0.72 to 2.03; P = 0.48). There were 29 cases among the 379 available participants in the dexrazoxane group and 23 cases among the 372 participants in the control group. ITT analyses demonstrated comparable results (753 participants). For more details, see Analysis 1.22.

Peripheral nervous system

Data on peripheral nervous system grade 3 or 4 toxicity (according to the CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-case analysis demonstrated no difference between the treatment groups (RR 0.68, 95% CI 0.12 to 3.98; P = 0.67). There were two cases among the 106 available participants in the dexrazoxane group and three cases among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.22.

Other effects

Adults

Liver damage

Data on severe liver damage (no definition provided) could be extracted from one study with a total of 108 participants (Sun 2016). The available-case analysis showed no difference between the treatment groups (RR 1.00, 95% CI 0.06 to 18.58; P = 1.0). There was one case among the 54 available participants in the dexrazoxane group and one case among 54 participants in the control group. ITT analyses demonstrated comparable results (110 participants). For more details, see Analysis 1.23.

Pain on injection

Data on pain on injection (grade 3 or 4 according to the ECOG criteria) could be extracted from two trials (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. four cases among the 249 participants in the dexrazoxane group and three cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 1.51, 95% CI 0.34 to 6.73; P = 0.59).

Phlebitis

Data on phlebitis could be extracted from three trials (Swain 1997a(088001); Swain 1997a(088006); Venturini 1996); however, we subdivided the analysis into two groups since the studies used different definitions. Swain 1997a(088001) and Swain 1997a(088006) defined phlebitis as grade 3 or 4 according to the ECOG criteria. Only the best-case scenario (i.e. four cases among the 249 participants in the dexrazoxane group and three cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 1.53, 95% CI 0.34 to 6.90; P = 0.58).

Venturini 1996 defined phlebitis as grade 3 or 4 according to the WHO criteria. There was no case among the 82 available participants in the dexrazoxane group and two cases among the 78 participants in the control group. We were not able to calculate a RR since there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 0.24). Best-case and worst-case scenarios showed comparable results (162 participants). For more details and data, see Table 3.

Anorexia

Data on anorexia (grade 3 or 4 according to the ECOG criteria) could be extracted from two trials (Swain 1997a(088001); Swain 1997a(088006)). Only the best-case scenario (i.e. 23 cases among the 249 participants in the dexrazoxane group and 27 cases among the 285 participants in the control group; total of 534 participants) was analysed since the number of missing data was unclear. The results showed no difference between the treatment groups (RR 0.97, 95% CI 0.57 to 1.65; P = 0.91).

Alopecia

Data on alopecia could be extracted from four studies (Marty 2006; Speyer 1992; Swain 1997a(088001); Swain 1997a(088006)); however, we subdivided the analysis into two groups since the studies used different definitions (see Characteristics of included studies).

First, the study of Speyer 1992 was analysed separately and the available-case analysis demonstrated no difference between the treatment groups (RR 1.02, 95% CI 0.91 to 1.13; P = 0.74). There were 69 cases among the 76 available participants in the dexrazoxane group and 66 cases among the 74 participants in the control group (150 participants in total). ITT analyses demonstrated identical results since there were no missing data.

The studies of Marty 2006, Swain 1997a(088001) and Swain 1997a(088006) used comparable criteria. The available-case analysis was based on the results of Marty 2006 with a total of 164 participants and showed no difference between the treatment groups (RR 1.19, 95% CI 0.64 to 2.24; P = 0.58). There were 18 cases among the 85 available participants in the dexrazoxane group and 14 cases among the 79 participants in the control group. ITT analyses demonstrated comparable results. The RR for the worst-case scenario was identical since there were no missing data in the study of Marty 2006. For the best-case scenario, the studies Swain 1997a(088001) and Swain 1997a(088006) were added which resulted in a total of 698 participants. The RR of the best-case scenario (i.e. 227 cases among 334 participants in the dexrazoxane group and 251 cases among 364 participants in the control group) was 1.01 (95% CI 0.94 to 1.09; P = 0.75). The studies Swain 1997a(088001) and Swain 1997a(088006) could only be added to the best-case scenario as the number of missing participants was unclear.

For more details, see Analysis 1.23.

Asthenia

Data on asthenia (grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). The available-case analysis showed no difference between the treatment groups (RR 0.93, 95% CI 0.13 to 6.44; P = 0.94). There were two cases among the 85 available participants in the dexrazoxane group and two cases among the 79 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Fatigue

Data on fatigue could be extracted from two studies (Marty 2006; Venturini 1996); however, as definitions were not comparable, we performed separate analyses.

Data on fatigue (grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). The available-case analysis showed no difference between the treatment groups (RR 2.79, 95% CI 0.30 to 26.25; P = 0.37). There were three cases among the 85 available participants in the dexrazoxane group and one case among the 79 participants in the control group. ITT analyses demonstrated identical results since there were no missing data.

Data on fatigue (grade 3 or 4 according to the WHO criteria) could be extracted from one study with a total of 160 available participants (Venturini 1996). There were four cases among the 82 available participants in the dexrazoxane group and zero cases among the 78 participants in the control group. We were not able to calculate a RR since there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 0.12). Best-case analysis showed an identical result, while the worst-case analysis showed a significant difference (P = 0.03) in favour of the control group (162 participants). For more details and data, see Table 3.

Bone pain

Data on bone pain (grade 3 or 4 according to the CTCAEv2 criteria) could be extracted from one study with a total of 164 participants (Marty 2006). There were zero cases among the 85 available participants in the dexrazoxane group and four cases among the 79 participants in the control group. We were not able to calculate a RR since there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 0.052).The best-case and worst-case scenarios showed identical results (see Table 3).

Hand-foot syndrome

Data on hand-foot syndrome (grade 3 or 4 according to the WHO criteria) could be extracted from one study with a total of 160 available participants (Venturini 1996). There was one case among the 82 available participants in the dexrazoxane group and no cases among the 78 participants in the control group. We were not able to calculate a RR since there was only one study available in which one of the treatment groups experienced no events. Therefore, we used Fischer's exact test instead (P = 1.00).The best-case and worstcase scenarios showed comparable results (see Table 3).

Children

Pulmonary

Data on pulmonary grade 3 or 4 toxicity (according to the CTCAEv2 criteria) could be extracted from one study with a total of 214 participants (P9425). The available-case analysis demonstrated a difference in favour of the control group (RR 4.42, 95% CI 1.30 to 15.05; P = 0.02). There were 13 cases among the 106 available participants in the dexrazoxane group and 3 cases among the 108 participants in the control group. ITT analyses demonstrated comparable results (216 participants). For more details, see Analysis 1.24.

Sensitivity analyses for the risk of bias criteria

The results of the sensitivity analyses were consistent among the trials and did not differ from the overall analyses for all meta-analyses.

DISCUSSION

Myocardial damage due to anthracycline chemotherapy is a considerable, serious problem. It reduces QoL and can even cause premature death. Also, when myocardial damage occurs during therapy, the maximum cumulative dose of anthracyclines needs to be limited, and as a result, the efficacy of anthracycline chemotherapy will be reduced. There is thus a need for cardioprotective strategies, such as the use of dexrazoxane. This is the third update of this Cochrane Review evaluating the existing evidence on dexrazoxane.

Summary of main results

We identified 13 RCTs that were eligible for inclusion in the review: eight in adults and five in children. With this update, we added one new RCT in adults and two new RCTs in children. To ascertain the efficacy of a cardioprotective intervention, the best study design – provided that the design and execution are correct – is a randomised controlled trial in which the only difference between intervention and control groups is the use of the cardioprotective intervention. Although non-randomised studies have been published, due to the high risk of bias associated with these study designs, we did not include them in this systematic review.

In contrast to previous versions of this review, we now present results separately for adults and children (i.e. participants less than 22 years of age). Because of differences in, for example, background risks of cardiac disease in these populations (Armstrong 2013; Feijen 2019b; Groenewegen 2020; Van Dalen 2006), developmental changes and differences in the body composition of children, results might not be (easily) interchangeable (Kearns 2003).

We summarise the results in adults and children by outcome below (see also Summary of findings 1 and Summary of findings 2).

For clinical heart failure, our meta-analysis in adults showed a benefit in favour of the use of dexrazoxane (RR 0.22, 95% CI 0.11 to 0.43; 7 studies). In children, we identified no difference in clinical heart failure between treatment groups (RR 0.20, 95% CI 0.01 to 4.19; 3 studies). Three paediatric studies also assessed cardiomyopathy/heart failure as the primary cause of death. None of the participants had this outcome, but two control group participants died as a result of cardiomyopathy/heart failure listed as a secondary cause of death. No difference between treatment groups was identified (RR 0.20, 95% CI 0.01 to 4.11).

For subclinical myocardial dysfunction and clinical heart failure combined, we performed two separate pooled analyses for the adult studies based on the definitions used: there was a benefit in favour of the use of dexrazoxane for both available-case metaanalyses (RR 0.37, 95% CI 0.24 to 0.56; 3 studies; and RR 0.46, 95% CI 0.33 to 0.66; 2 studies, respectively). The paediatric studies also used different definitions, precluding a pooled analysis. One study showed a benefit in favour of the use of dexrazoxane (RR 0.33, 95% CI 0.13 to 0.85), whereas another study showed no difference between treatment groups (RR not estimable; best-case analysis only).

However, an important question regarding any cardioprotective intervention during anthracycline therapy is whether the cardioprotective drug could decrease the cardiotoxicity by anthracyclines without reducing the antitumour efficacy and without negative effects on toxicities other than cardiac damage. The antitumour efficacy is reflected by survival and tumour response rate. Overall survival and progression-free survival were only reported in adult RCTs (no new data in the update) and overall mortality was only reported in paediatric RCTs (all newly included in the update). The meta-analyses of both overall survival in adults and overall mortality in children showed no difference between the treatment groups (HR 1.04, 95% 0.88 to 1.23; 4 studies, and HR 1.01, 95% CI 0.72 to 1.42; 3 studies, respectively). We pooled the results on progression-free survival into one meta-analysis in the previous update, which demonstrated no difference between the treatment groups. However, after re-evaluating the definitions used in the different studies, in this update, we deemed them to be too heterogeneous to pool. We subdivided progression-free survival into three analyses based on the comparability of the definitions. We found a longer progression-free survival in favour of the use of dexrazoxane in one study (HR 0.62, 95% CI 0.43 to 0.90) and we found no difference between the treatment groups for the other two analyses (HR 0.95, 95% CI 0.64 to 1.40; 1 study, and HR 1.18, 95% CI 0.97 to 1.43; 2 studies, respectively). In adults, there was no difference in tumour response rate between treatment groups (RR 0.91, 95% CI 0.79 to 1.04; 6 studies, available-case analysis; no new data in the update). We subdivided tumour response rate in children into two analyses based on the comparability of definitions and identified no difference between treatment groups (RR 1.01, 95% CI 0.95 to 1.07; 1 study, only best-case analysis; and RR 0.92, 95% CI 0.84 to 1.01; 1 study, available-case analysis, respectively).

One of the most important adverse effects to investigate is the occurrence of secondary malignant neoplasms (SMN). Thus far, only paediatric studies have assessed this outcome. Since the previous update of this review, two studies could be added to the pooled analysis. The direction of effect remained the same, but the difference between the treatment groups changed in some analyses. The available- and worst-case analyses were identical and showed a difference in favour of the control group (RR 3.08, 95% CI 1.13 to 8.38; 3 RCTs). In the best-case analysis (the only analysis performed in the previous update) a fourth study could be added. It showed the same direction of effect but the result was not different between treatment groups (RR 2.51, 95% CI 0.96 to 6.53, 4 RCTs).

Regarding the other adverse effects (grade 3 or higher), it was possible to pool data for some adverse effects (available-case, bestcase and/or worst-case analyses), but

for others, only descriptive results are available. Compared to the second update of this review (Van Dalen 2011), we have added data on the adverse effects hand-foot syndrome, myelosuppression and liver damage for adults. We have added data on the following adverse effects for children: abnormal lymphocytes, haemoglobin, white blood cell count, platelets, absolute neutrophil count, haematological effects, sepsis, infection, allergic reaction, nausea, vomiting, mucositis and central nervous system effects.

In adults, there was a higher risk of abnormal white blood cell count at nadir in the dexrazoxane group. The haematologic effects that showed no difference between treatment groups were thrombocytopenia, neutropenia, abnormal granulocyte count at nadir and at recovery, abnormal white blood cell count at recovery, abnormal platelet count at nadir and at recovery, anaemia, myelosuppression (one study) and leukopenia. All analyses included two pooled studies unless otherwise stated. In children, there was a higher risk of abnormal haemoglobin (two individual studies) and abnormal white blood cell count (one study) in the dexrazoxane group. For both platelets (either a difference in favour of the control group (one study) or no difference between treatment groups (one study)) and absolute neutrophil count (a difference in favour of the control group in most analyses, but no difference in one analysis; two individual studies), inconsistent results were identified. The following haematologic effects showed no difference between treatment groups: lymphocytes (one study), thrombosis (one study), and haematological effects (one study).

None of the immune system/infectious effects showed a difference between the treatment groups. In adults, fever (two pooled studies; one individual study), febrile bone marrow aplasia (one study), febrile neutropenia (one study), fever with either positive blood or other cultures (both one study) and pyrexia (one study) were evaluated. In children, sepsis (two individual studies), infection (two pooled studies (unexplained heterogeneity was identified) and one individual study), and allergic reaction (two individual studies) were evaluated.

In adults, for nausea the best-case analysis demonstrated a lower risk of nausea in the dexrazoxane group (three pooled studies), but the available- and worst-case analysis demonstrated no difference between treatment groups (both one study); one individual study showed no difference between treatment groups irrespective of type of analysis. The gastrointestinal effects that showed no difference between treatment groups were vomiting (three pooled studies best-case analyses, other analyses one study; one individual study), nausea and vomiting (two individual studies), stomatitis (one individual

study; two pooled studies; three pooled studies best-case analyses, other analyses one study), diarrhoea (two individual studies and two pooled studies), constipation (one study), and mucosal inflammation (one study). In children, there was a lower risk of mucositis in the dexrazoxane group (one study). The following effects showed no difference between treatment groups: nausea, vomiting, nausea or vomiting, stomatitis and typhlitis (all in one study).

None of the neurological effects showed a difference between the treatment groups. These outcomes were neurotoxicity in adults (two pooled studies; unexplained heterogeneity was identified) and central and peripheral nervous system in children (two pooled studies and one individual study, respectively).

For other effects, in adults, none of the other effects showed a difference between the treatment groups. These were liver damage (one study), pain on injection (two pooled studies), phlebitis (two pooled studies; one individual study), anorexia (two pooled studies), alopecia (one individual study and three pooled studies), asthenia (one study), and bone pain (one study). For fatigue (two individual studies), only in a worst-case analyses was a difference in favour of the control group identified. In children, there was a higher risk of pulmonary effects in the dexrazoxane group (one study).

In summary, for adverse effects other than cardiac and SMN, results varied. For some haematological effects (adults and children), pulmonary effects (children) and other effects (adults), there was a difference in favour of the control group, although not always consistent in all analyses. For some gastrointestinal effects (adults and children), there was a difference in favour of the dexrazoxane group, but again not always consistent in all analyses. For most adverse effects, no difference between treatment groups was identified.

It should be noted that data were not available for all outcomes of interest. None of the included studies evaluated quality of life.

Overall completeness and applicability of evidence

The evidence from adults demonstrated a cardioprotective effect of dexrazoxane. The evidence in children is less clear; only for one cardiac outcome was a difference reached. However, 'no evidence of effect' is not the same as 'evidence of no effect'. The reason that no difference between treatment groups was identified could be, as with all other outcomes, due to the number of participants included in these studies being too small

to detect a difference (i.e. low power). Also, anthracycline-induced cardiotoxicity is dose-dependent (Feijen 2019b), and in some of the studies participants received a relatively low cumulative anthracycline dose. Furthermore, heart failure can develop not only during anthracycline therapy, but also years after the end of treatment (Armstrong 2013; Feijen 2019b), so the length of followup could have been too short to detect a difference between the treatment groups.

At the moment, dexrazoxane is not routinely used in children and adults who receive anthracyclines as part of their cancer treatment. This caution might be driven by the suspicion of interference with antitumour efficacy (that is, tumour response rate and survival) and by the occurrence of SMN.

Our (meta-)analyses of antitumour efficacy either showed results in favour of the dexrazoxane group or no difference between participants who were treated with or without dexrazoxane (in children, PFS was not evaluated). Also, the value of tumour response rate for predicting survival is not clear (Cooper 2020; Odaimi 1987; Pierga 2001). In our (meta-)analyses of both OS and PFS, either a difference in favour of the dexrazoxane group (which included the individual study which identified a difference in tumour response rate (Swain 1997a(088001)) was found or no difference between the dexrazoxane and control group. It should be noted that the study that identified a difference in PFS in favour of the dexrazoxane group used a rather unconventional definition (i.e. time from first date of complete response, partial response or stable disease until the date progressive disease was first noticed). We cannot be sure how that affected the results.

Only paediatric RCTs evaluated SMN and the results were slightly different depending on the analysis method used (i.e. availablecase, best-case, worst-case), but the direction of effect, in favour of the control group, was the same in all analyses. Although we cannot rule out that dexrazoxane might increase the risk of SMN, when interpreting these results it should be kept in mind that, although the only difference between treatment groups in these RCTs should have been the presence or absence of dexrazoxane, it is possible that other factors influenced the occurrence of SMN.

For example, etoposide is associated with an increased risk of SMN (Le Deley 2003; Seif 2015; Travis 2013). In some of the included studies, participants did receive etoposide (P9425; P9426), possibly with different cumulative doses in the dexrazoxane and control groups. Etoposide, anthracyclines and dexrazoxane all interfere with topoisomerase II and, hypothetically, this combination may have a synergistic effect on cell proliferation

as suggested by an in vitro study on cardiotoxicity (Nemade 2018). Topoisomerase inhibitors are associated with secondary haematologic malignancies, such as acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), which mainly occur within three years after therapy. The latency time of secondary solid tumours caused by chemotherapy is more than 10 years (Hawkins 2020). The median follow-up time of the studies evaluating SMN ranged from 4.6 to 9.4 years; for some included participants, followup was only 0.01 year.

Radiation therapy is also an important risk factor of SMN (Hawkins 2020). Again, in some of the included studies, participants did receive radiation therapy, possibly with differences between the dexrazoxane and control groups. And some of the identified SMN are located within the radiation field. So we cannot exclude the possibility that radiation therapy plays a role in the occurrence of SMN in our included studies.

The same is true for other potential risk factors for SMN, such as other chemotherapeutic agents and genetic susceptibility (Turcotte 2018).

Unfortunately, there are too few included studies to reliably perform subgroup analyses in order to further investigate reasons for the possible increased risk of SMN in the dexrazoxane group (Higgins 2011); the risk of possible confounding should also not be forgotten. However, when analysing only studies that included etoposide in their treatment regime (P9425; P9426), or studies that included cranial irradiation (DFCI 95-01; P9404), the direction of effect remained the same (results not shown).

It should be noted that, although there might be a higher risk of SMN in children treated with dexrazoxane, mortality due to a second cancer did not differ between treatment groups according to a publication addressing three of the four paediatric studies with SMN data included in this review (P9404; P9425; P9426; Chow 2015 reference): HR 1.24 (95% CI 0.49 to 3.15). This result was based on 10 SMN deaths in the dexrazoxane group and 8 in the control group after a median follow-up of 12.4 years. A more recent study by Chow and colleagues showed similar results when including data from all four paediatric RCTs included in this review: HR 1.17 (95% CI 0.51 to 2.70; 12 SMN deaths in the dexrazoxane group and 10 in the control group), but only approximately 28% of participants from the DFCI 95-01 study could be included (Chow 2021). The median follow-up duration for this outcome is not completely clear, but might be 18.6 years as reported for the study overall. Unfortunately, at the moment, no data on the total number of SMN cases (so not only deaths) with increased follow-up are available to update the current analysis.

In one of the five paediatric studies and in three of the eight adults studies, participants in the intervention and control groups received comparable cumulative anthracycline doses. Although according to the review's protocol, participants in both treatment groups should have received the same anthracycline dose, the actual received cumulative dose was not reported in three paediatric studies. However, in these three paediatric studies, the following information was reported: all participants received the same cumulative dose (P9404); the received dose was in high compliance with prescribed dose (P9426); and there were virtually no dose reductions (P9425). In one paediatric study (Wexler 1996), and in one adult study (Speyer 1992), participants in the dexrazoxane group received a higher cumulative anthracycline dose (100 mg/m2 or more) than participants in the control group. So despite a higher cumulative anthracycline dose received in the dexrazoxane group, there was still a lower rate of cardiotoxicity. In four adult studies, it was unclear if participants in the intervention and control groups received similar cumulative anthracycline doses. If participants in the control group received a higher cumulative anthracycline dose than participants treated with dexrazoxane, this could have led to an overestimation of the cardioprotective effect of dexrazoxane (and vice versa). This uncertainty should also be kept in mind when interpreting the results of the secondary outcomes (tumour response rate, survival and adverse effects).

In the included studies, different ratios of dexrazoxane to anthracyclines were used. We did not analyse the effect of these different ratios on the outcomes.

The applicability of our results to current clinical practice might be limited since the majority of the included studies were executed at the end of last century. Supportive care and anticancer treatments have since improved considerably.

Finally, data were not available for all outcomes of interest. As a result, we cannot draw conclusions regarding those outcomes, but they are of course important for clinical practice.

We are awaiting (additional) results of the currently ongoing study (N = 1) and the studies which await classification (N = 12).

Quality of the evidence

In adults, we graded the quality of the evidence as moderate for almost all evaluated outcomes (downgraded one level for study limitations). We graded two of the three PFS outcomes (using different definitions) as low (downgraded an additional level for imprecision); we graded the third PFS outcome/definition as moderate.

In children, we graded the quality of the evidence as low for almost all evaluated outcomes (downgraded either two levels for study limitations or one level for study limitations and one level for imprecision). We graded two outcomes as very low quality (one definition of clinical heart failure and subclinical myocardial dysfunction combined and one definition of tumour response rate) (downgraded two levels for study limitations and one level for imprecision).

In many studies, bias could not be ruled out due to lack of reporting. However, this is the best evidence available now from RCTs evaluating dexrazoxane as a cardioprotective intervention in children and adults with cancer treated with anthracyclines.

Potential biases in the review process

This systematic review used a very broad search strategy for identifying eligible studies. Thus, although it is unlikely that we missed eligible studies, it is never possible to completely rule out reporting bias.

Since the search strategy included search terms for cardiotoxicity, it is possible that for outcomes other than cardiotoxicity, more evidence is available than identified in this review. Also, in this systematic review, cardiotoxicity was evaluated as a binary outcome; that is, the number of participants below and above the cut-off value for an abnormal result. Some studies have evaluated cardiotoxicity as a continuous outcome, but in doing so, it is possible that participants with good and bad values balance each other out, resulting in an adequate mean value. This can give the impression that there is no problem, while for some participants this might not be true. Therefore, we did not include these data.

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analyses showed the efficacy of dexrazoxane in preventing or reducing cardiotoxicity in adults treated with anthracyclines. In children, there was only a difference between treatment groups for one of the cardiac outcomes (in favour of dexrazoxane). In adults, no evidence of a negative effect on tumour response rate, overall survival (OS) and progression-free survival (PFS) was identified. In children, no evidence of a negative effect on tumour response rate and overall mortality was identified. The results for adverse effects varied, but there might be a higher risk of some haematological effects (adults

and children) and pulmonary effects (children) and a lower risk of some gastrointestinal effects (adults and children) for those treated with dexrazoxane compared to control. Children treated with dexrazoxane might have a higher risk of secondary malignant neoplasms (SMN); in adults, this outcome was not addressed. In adults, the quality of the evidence ranged between moderate and low; in children, between low and very low.

We conclude that if the risk of cardiac damage is expected to be high, it might be justified to use dexrazoxane in children and adults with cancer treated with anthracyclines. However, clinicians and patients should weigh the cardioprotective effect of dexrazoxane against the possible risk of adverse effects, including SMN, for each individual. For children, the International Late Effects of Childhood Cancer Guideline Harmonization Group has developed a clinical practice guideline (De Baat 2022).

The full version of this review, including characteristics of studies, all data and analyses, additional tables and search strategies, can be found online in: Cochrane Database Syst Rev. 2022 Sep 27;9(9):CD014638. doi: 10.1002/14651858.CD014638.pub2.

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* Indicates the major publication for the study

5.2

PRIMARY CARDIOPROTECTION WITH DEXRAZOXANE IN CHILDHOOD CANCER PATIENTS EXPECTED TO RECEIVE ANTHRACYCLINES: RECOMMENDATIONS FROM THE INTERNATIONAL LATE EFFECTS OF CHILDHOOD CANCER GUIDELINE HARMONIZATION GROUP

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The Lancet Child & Adolescent Health. 2022 Dec;6(12):885-894

SUMMARY

Survivors of childhood cancer are at risk of anthracycline-induced cardiotoxicity, which might be prevented by dexrazoxane. However, concerns exist about the safety of dexrazoxane, and little guidance is available on its use in children. To facilitate global consensus, a working group within the International Late Effects of Childhood Cancer Guideline Harmonization Group reviewed the existing literature and used evidence-based methodology to develop a guideline for dexrazoxane administration in children with cancer who are expected to receive anthracyclines. Recommendations were made in consideration of evidence supporting the balance of potential benefits and harms, and clinical judgement by the expert panel. Given the dose-dependent risk of anthracycline-induced cardiotoxicity, we concluded that the benefits of dexrazoxane probably outweigh the risk of subsequent neoplasms when the cumulative doxorubicin or equivalent dose is at least 250 mg/m^2 (moderate recommendation). No recommendation could be formulated for cumulative doxorubicin or equivalent doses of lower than 250 mg/m^2, due to insufficient evidence to determine whether the risk of cardiotoxicity outweighs the possible risk of subsequent neoplasms. Further research is encouraged to determine the long-term efficacy and safety of dexrazoxane in children with cancer.

INTRODUCTION

5-year survival rates in patients with childhood cancer in high-income countries have increased to greater than 80%[1], which has led to an increasing number of survivors who reach adulthood. Despite this progress, survivors of childhood cancer are at risk of developing myocardial dysfunction that is predominantly caused by the cardiotoxic effects of anthracycline analogues (doxorubicin, daunorubicin, epirubicin, and idarubicin), mitoxantrone, and radiotherapy exposure of the heart[2-7]. Myocardial dysfunction can lead to clinically overt heart failure and is associated with increased mortality[8,9]. 30 years after cancer treatment in a Dutch cohort of 6165 childhood cancer survivors diagnosed between 1963 and 2002, the cumulative incidence of heart failure approached 4% in childhood cancer patients treated with a doxorubicin equivalent dose of lower than 250 mg/m^2, and exceeded 13% in those treated with 250 mg/m^2 or higher[2].

Although research has shown that anthracyclines can be safely removed from treatment regimens for some patients[10], these drugs remain an important component of curative therapy for many childhood cancers[11]. Therefore, extensive research has aimed to identify interventions that prevent or reduce anthracycline-induced myocardial dysfunction[12-14]. Dexrazoxane (sold as Cardioxane, ICRF-187 [Clinigen Healthcare, Stafford, UK]; or Zinecard, ADR-529 [Pharmacia & Upjohn, Pfizer, New York, NY, USA]) is one of the most widely investigated cardioprotective pharmacological interventions. The exact mechanism of dexrazoxane cardioprotection is not fully understood. Current research suggests that dexrazoxane interferes with the pathophysiological mechanisms of anthracyclines by chelation of iron and transient binding with topoisomerase receptors[15-17].

Dexrazoxane has been available as a cardioprotectant since the 1990s, but there is variation in clinical practice guidance and use in children. There is no international guideline on the use of this drug in children with cancer[18-20]. To facilitate global consensus regarding this topic, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) convened a group of international experts to develop a transparent evidence-based clinical practice guideline for dexrazoxane administration in children with cancer (aged ≤21 years for the purpose of the guideline) who will be treated with anthracyclines.

IGHG GUIDELINE DEVELOPMENT PROCESS

Guideline panel formation

A panel of 20 international specialists in paediatric haematology-oncology, paediatric cardiology, pharmacology, epidemiology, and guideline methodology was convened (appendix p 2). Members were invited on the basis of their experience and knowledge on the topic. An overview of the process of guideline development is presented in the appendix (p 3).

Scope and definitions

The aim of this clinical practice guideline is to provide guidance to health-care providers about when to administer dexrazoxane concurrently with anthracyclines in patients who are diagnosed with cancer at age 21 years or younger, taking into consideration the existing evidence regarding the benefits and harms associated with its use. The benefits of dexrazoxane are provided by its ability to reduce adverse cardiac outcomes, which include clinical heart failure, subclinical myocardial dysfunction, and cardiac mortality. The consideration of harms included the potential for dexrazoxane to have a negative effect on the oncological efficacy of treatment with anthracyclines (decreased tumour response, progressive disease) and thereby possibly reducing survival, and clinically significant adverse effects other than cardiac toxicity (eg, subsequent malignant neoplasms). Our panel formulated the following clinical questions: what is the effect of dexrazoxane administration compared with no dexrazoxane or placebo during anthracycline chemotherapy on cardiotoxicity in children with cancer; and what is the effect of dexrazoxane administration compared with no dexrazoxane or placebo during anthracycline chemotherapy on safety outcomes in children with cancer.

Literature search and selection

To develop this guideline, we included evidence from both randomised controlled trials (RCTs) and non-randomised studies. For evidence from RCTs, we used a recently updated Cochrane systematic review on the effects of dexrazoxane, which also includes a detailed description of the methods used[21]. Eligible study populations were patients with childhood and adult cancer treated with anthracyclines with or without dexrazoxane. Outcomes of interest for efficacy included clinical heart failure, subclinical myocardial dysfunction (which could be defined as either abnormalities in cardiac function measured by imaging [echocardiography, radionuclide ventriculography, or cardiac magnetic resonance

imaging] or histological abnormalities scored by the Billingham score on endomyocardial biopsy), and cardiac mortality (death due to cardiomyopathy or heart failure). For safety, outcomes included tumour response (defined as the number of complete and partial remissions), progression-free survival, overall mortality or survival, quality of life, and toxicities other than cardiac damage (eg, subsequent malignant neoplasms, alopecia, nausea, vomiting, stomatitis, diarrhoea, fatigue, anaemia, leukopenia, and thrombocytopenia).

Because the evidence from RCTs in children was scarce, we performed an additional systematic search using MEDLINE (through PubMed) from Jan 1, 1966 to July 12, 2021 to identify non-randomised studies that compared patients who received anthracyclines with and without dexrazoxane. Studies were included if at least 75% of the study patients had been diagnosed with cancer at the age of 21 years or younger, and if the sample comprised at least 50 patients in each treatment group. Outcomes of interest were identical to those in the Cochrane systematic review[21]. Full details on the search strategies and inclusion criteria used to answer each clinical question are provided in the appendix (p 4).

Studies meeting the inclusion criteria for non-randomised studies were selected by two of the three independent reviewers (ECdB, ECvD, and RLM). Detailed information from each eligible study was extracted into evidence tables and collated in summary of findings tables.

The (pooled) analyses in the Cochrane systematic review were performed using the Review Manager 5 software provided by Cochrane, according to the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions. We performed a meta-analysis if two or more comparable studies were identified. If this was not the case, we summarised results descriptively. For outcomes where only one study was available and we were unable to calculate a RR as one of the treatment groups experienced no events, we used Fischer's exact test instead[21].

If outcome assessments were not available for all participants, we performed an available-case analysis and, if possible, also a best-case and worst-case analysis. The available-case analysis only includes participants who had an outcome assessment; the best-case analysis includes all participants and usually assumes that participants without an outcome assessment did not develop the outcome (eg, heart failure), whereas the worst-case analysis includes all participants and usually assumes that all participants without an outcome assessment developed the outcome. However, for tumour response

rate (ie, number of participants with a remission) this is the opposite: due to the nature of this outcome, best case here means that the participant does have the outcome[21].

Translating evidence into recommendations

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Evidence to Decision framework was used to formulate recommendations in a systematic and transparent manner[22]. The importance of efficacy and safety outcomes was scaled and a hierarchy was defined (appendix p 5). The quality of the total body of evidence was assessed by the GRADE approach[23] and the strength of the recommendations was graded according to published evidence-based methods (appendix p 6). The current guideline focuses on children and adolescents; therefore, we downgraded studies in adults (aged >21 years) by one level (ie, from high quality to moderate quality, from moderate quality to low quality, or from low quality to very low quality) to account for indirectness to extrapolate the evidence to children[24]. Recommendations were based on consideration of evidence, the balance of potential benefits and harms, and clinical judgements of the expert panel. Decisions were made through group discussion and consensus.

Evidence from the literature review

The Cochrane systematic review included 13 randomised controlled trials (RCTs). Five RCTs were categorised as paediatric studies (n=1252) and eight RCTs were categorised as adult studies (n=1269; appendix p 7). Detailed information on the included studies is provided in the Cochrane systematic review[21]. Our literature review for non-randomised studies identified 195 potentially relevant abstracts, of which five studies were eligible for inclusion (figure, appendix p 8). Detailed information on included non-randomised studies is provided in evidence tables and summary tables in the appendix (pp 9–23). Conclusions of the RCTs and non-randomised studies are summarised in the table.

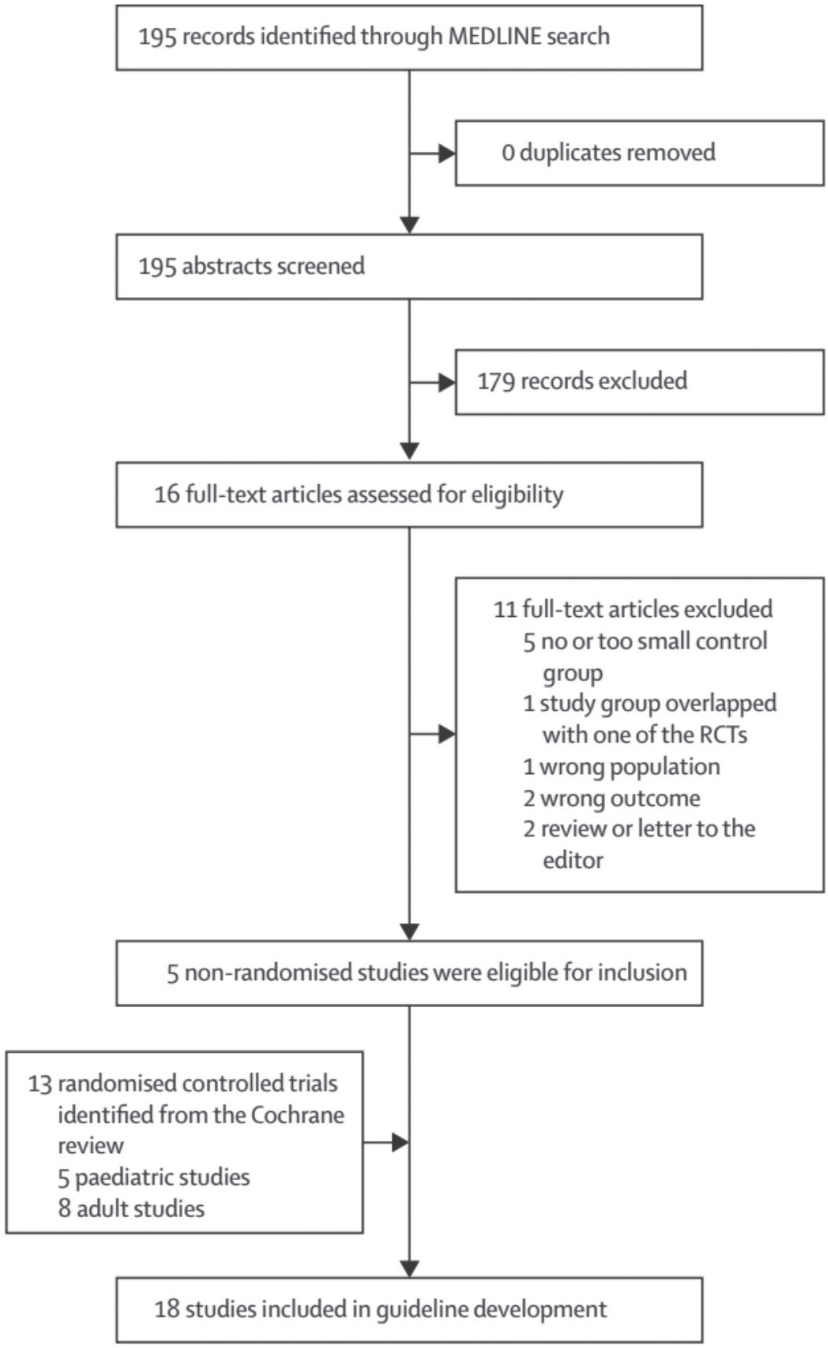

Figure: Study selection

Efficacy outcomes

Pooled analysis of three RCTs in children showed no significant difference in clinical heart failure risk related to anthracyclines between patients treated with and without dexrazoxane (risk ratio [RR] 0·20, 95% CI 0·01-4·19; low-quality evidence)[21,25-27]. Pooled analysis from seven RCTs in adults showed that patients treated with dexrazoxane were less likely to develop clinical heart failure than patients treated without dexrazoxane (RR 0·22, 0·11-0·43; moderate-quality evidence; low-quality evidence for children)[21,28-34]. Furthermore, two non-randomised studies in children both showed no significant difference in clinical heart failure with or without dexrazoxane (very low-quality evidence)[35,36].

The outcome of clinical heart failure and subclinical myocardial dysfunction combined was assessed by two RCTs in children. However, the results could not be pooled due to differences in definitions for outcomes of interest (table). One RCT showed that children treated with dexrazoxane were less likely to develop clinical heart failure or subclinical myocardial dysfunction than those treated without dexrazoxane (RR 0·33, 0·13–0·85; low-quality evidence)[21,38]. In this RCT, the dexrazoxane group received a 100 mg/m^2 higher median cumulative anthracycline dose compared with the control group. The other RCT showed no significant difference in children treated with dexrazoxane versus those treated without dexrazoxane (very low-quality evidence; Fischer's exact test p=0·12)[21,25].

Based on outcome definitions for clinical heart failure and subclinical myocardial dysfunction, two separate pooled analyses were performed for the RCTs in adults. Both analyses showed that patients treated with dexrazoxane were less likely to develop clinical heart failure or subclinical myocardial dysfunction (RR 0·37, 0·24–0·56; moderate-quality evidence; [21,28,29,34] and RR 0·46, 0·33–0·66; moderate-quality evidence, [21,32,33] respectively; both low-quality evidence for children).

Two of four non-randomised studies in children showed no significant difference in rates of clinical heart failure and subclinical myocardial dysfunction combined[36,39], whereas the other two studies showed a significantly lower combined risk of clinical heart failure and myocardial dysfunction in patients treated with dexrazoxane (very low-quality evidence)[35,40].

Three RCTs in children evaluated cardiomyopathy or heart failure as the primary cause of death. None of the included participants developed such an event, so the relative effect of dexrazoxane was not estimable (low-quality evidence)[21,37].

Safety outcomes

Tumour response was assessed by two RCTs in children. However, the results could not be pooled due to differences in definitions for outcomes of interest (table). Both RCTs showed no difference between the (RR 1·01, 95% CI 0·95–1·07, very low-quality evidence; [21,41] and RR 0·92, 95% CI 0·84–1·01, low-quality evidence[21,27]).

Tumour response was also assessed in six RCTs in adults. Pooled analysis showed no significant difference in adults treated with dexrazoxane versus those treated without dexrazoxane (RR 0·91; 95% CI 0·79–1·04; moderate-quality evidence; low-quality evidence for children)[21,28-30,32-34].

Progression-free survival was only assessed in four RCTs in adults, and the analyses were divided into three different groups according to definitions used for the outcome of interest (table). For one definition, study data showed a significant difference in favour of patients treated with dexrazoxane (hazard ratio [HR] 0·62, 95% CI 0·43–0·90; low-quality evidence; very low-quality evidence for children)[21,29]. Analysis according to the other two definitions showed no significant difference between adults treated with and without dexrazoxane (HR 0·95, 0·64–1·40; low-quality evidence, very low-quality evidence for children [one RCT][21,30]; and pooled HR 1·18, 0·97–1·43; moderate-quality evidence, low-quality evidence for children [two RCTs][21,32,33]).

Data from three RCTs in children showed no significant difference in overall mortality between the groups treated with and without dexrazoxane (HR 1·01, 0·72–1·42; low-quality evidence)[21,37]. Additionally, data from four RCTs in adults showed no significant difference in overall survival when anthracyclines were administered with or without dexrazoxane (HR 1·04, 0·88–1·23; moderate-quality evidence; low-quality evidence for children) [21,29,30,32,33]. Two non-randomised studies in children also showed no significant difference in overall survival (very low quality evidence)[35,36].

Data on subsequent malignant neoplasms could be extracted from four RCTs in children. As described in the Cochrane review [21], three types of pooled analyses were performed (ie, available-case, worst-case, and best-case analyses) to account for missing data. The available-case and worst-case analyses were identical and showed that children treated with dexrazoxane were more likely to develop subsequent malignant neoplasms than those not treated with dexrazoxane (RR 3·08, 1·13–8·38; low-quality evidence [three RCTs])[21,25,27,42]. For the best-case analysis, the remaining RCT with subsequent malignant neoplasm data could be added. This analysis showed the same direction of effect, but

without a significant difference in subsequent malignant neoplasms between the groups treated with and without dexrazoxane (RR 2·51, 0·96–6·53; low-quality evidence)[21,25,27,42,43].

Three non-randomised studies in children evaluated the risk of subsequent malignant neoplasms. Two studies showed no significant difference between children treated with and without dexrazoxane, and in the third study, subsequent malignant neoplasm risk was unclear as the number of patients with assessment of subsequent malignant neoplasm was not provided (all very low-quality evidence)[35,36,,44]. The appendix (pp 24–25) provides an overview of the subsequent malignant neoplasm cases in children with detailed information on primary diagnosis and treatment.

Ten studies evaluated the risk of developing multiple severe or life-threatening adverse events other than cardiotoxicity or subsequent malignant neoplasms[21,25,27-33,45]. We classified the adverse events into the following groups: haematological effects, immune system and infectious effects, gastrointestinal effects, neurological effects, and other (appendix p 26). The exact definitions used are included in the Cochrane systematic review[21]. Data from RCTs in children showed that patients treated with dexrazoxane were more likely to develop abnormal haemoglobin, white blood cell count, and pulmonary toxicity (one to two studies per outcome). Effects on platelets and neutrophil count were inconsistent between studies. Data from two RCTs in adults showed that patients treated with dexrazoxane were more likely to develop low white blood cell count at nadir than those treated without dexrazoxane. Other reported adverse effects in RCTs in children or adults were either in favour of the dexrazoxane group, or no significant difference was evident between treatment groups. One non-randomised study in children showed no significant difference for all evaluated events during cancer treatment[35]. Exact information on the timing from exposure and persistence of these effects were not provided by the RCTs, but it is likely that these were acute, transient effects during cancer treatment.

Table: Conclusions of evidence on the effects of anthracycline treatment with versus without dexrazoxane

	Conclusion	Effect (95% CI) or p value* dexrazoxane vs no dexrazoxane	GRADE - quality of evidence for children
Clinical heart failure			
Children, RCT	No significant difference between treatment groups	Pooled RR 0.20 (0.01 – 4.19)	Low (three studies)[25-27]
Adults, RCT	Lower risk in dexrazoxane treated group	Pooled RR 0.22 (0.11 – 0.43)	Low† (seven studies)[28-34]
Children, observational	No significant difference between treatment groups	Single studies	Very low (two studies)[35,36]
Cardiomyopathy/heart failure as primary cause of death			
Children, RCT	No events in both treatment groups	Not estimable	Low (three studies)[37]
Adults, RCT	No studies	No studies	No studies
Children, observational	No studies	No studies	No studies
Clinical heart failure and subclinical myocardial dysfunction combined			
Children, RCT	Lower risk in dexrazoxane treated group (definition 1‡)	RR 0.33 (0.13 – 0.85)	Low (one study)[38]
Children, RCT	No significant difference between treatment groups (definition 2§; best-case analysis)	Fisher's exact test p=0.12	Very low (one study)[25]
Adults, RCT	Lower risk in dexrazoxane treated group (definition 1‡)	Pooled RR 0.37 (0.24 – 0.56)	Low† (three studies)[28,29,34]
Adults, RCT	Lower risk in dexrazoxane treated group (definition 2§)	Pooled RR 0.46 (0.33 – 0.66)	Low† (two studies)[32,33]
Children, observational	Lower risk in dexrazoxane treated group	Single studies	Very low (four studies)[35,36,39,40]
Tumor response			
Children, RCT	No significant difference between treatment groups (definition 1¶; best-case analysis)	RR 1.01 (0.95 – 1.07)	Very low (one study)[41]
Children, RCT	No significant difference between treatment groups (definition 2‖)	RR 0.92 (0.84 – 1.01)	Low (one study)[27]
Adults, RCT	No significant difference between treatment groups	Pooled RR 0.91 (0.79 – 1.04)	Low† (six studies)[28-30,32-34]
Children, observational	No studies	No studies	No studies
Progression-free survival			
Children, RCT	No studies	No studies	No studies
Adults, RCT	In favor of dexrazoxane treated group (definition 1**)	HR 0.62 (0.43 – 0.90)	Very low† (one study)[29]
Adults, RCT	No significant difference between treatment groups (definition 2††)	HR 0.95 (0.64 – 1.40)	Very low† (one study)[30]
Adults, RCT	No significant difference between treatment groups (definition 3‡‡)	Pooled HR 1.18 (0.97 – 1.43)	Low† (two studies)[32,33]
Children, observational	No studies	No studies	No studies

	Conclusion	Effect (95% CI) or p value* dexrazoxane vs no dexrazoxane	GRADE - quality of evidence for children
Overall survival or mortality			
Children, RCT	No significant difference in mortality between treatment groups	Pooled HR 1.01 (0.72 – 1.42)	Low (three studies)[37]
Adults, RCT	No significant difference in survival between treatment groups	Pooled HR 1.04 (0.88 – 1.23)	Low† (four studies)[29,30,32,33]
Children, observational	No significant difference in survival between treatment groups	Single studies	Very low (two studies)[35,36]
Adverse effects: subsequent malignant neoplasm			
Children, RCT	Higher risk in dexrazoxane treated group (in available-case and worst-case analyses)	Pooled RR 3.08 (1.13 – 8.38; identical from available-case and worse-case analyses)	Low (three studies)[25,27,42]
Children, RCT	No significant difference between treatment groups (best-case analysis)	Pooled RR 2.51 (0.96 – 6.53)	Low (four studies)[25,27,42,43]
Adults, RCT	No studies	No studies	No studies
Children, observational	No significant difference between treatment groups	Single studies	Very low (three studies)[35,36,44]

See appendix pp 18–23 for summary tables with statistical results per outcome for the observational studies.

HR=hazard ratio. LVEF=left ventricular ejection fraction. LVFS=left ventricular fractional shortening. MUGA=multigated acquisition scan. RCT=randomised controlled trials. RR=risk ratio. *Results from available case analysis (available-case, worst-case, and best-case analyses showed similar results if only one analysis result is provided). †Quality of the evidence from adult RCTs was downgraded by one level to account for indirectness. ‡Definition 1 is evidence of clinical congestive heart failure, a reduction in LVEF (as measured by MUGA) to <45%, or a decrease in LVEF (as measured by MUGA) of >20 percentage points from baseline. §Definition 2 is clinical heart failure (no definition provided) or subclinical myocardial dysfunction defined as decreased LVFS (however, the authors stated that toxicity was graded according to NCI CTCAEv2 criteria, but LVFS is not included in that definition). ¶For definition 1 of complete remission, no definition was provided. ‖Definition 2 is the disappearance of active Hodgkin lymphoma (gallium negative, ≥70% decrease in the sum of the products of the perpendicular diameters of measurable lesions, and negative bone marrow or bone scan if initially positive). **Definition 1 is time from first date of complete response, partial response, or stable disease until the date progressive disease was first noticed. ††Definition 2 is time to progression (starting point not mentioned). ‡‡Definition 3 is time from randomisation to progression either on or off treatment.

RECOMMENDATIONS

The benefits and harms of dexrazoxane based on the available evidence are summarised in panel 1, and the complete Evidence-to-Decision framework is presented in the appendix (pp 27–29). Although there is consistent evidence that treatment with dexrazoxane results in less cardiotoxicity than treatment without dexrazoxane, it is not routinely used in clinical practice because of previous and ongoing uncertainties regarding its safety. Potential harms include the risk of reduced survival, tumour response, progression of disease, and other adverse effects such as subsequent malignant neoplasms. Consideration of the threshold at which benefits outweigh harms is important.

Panel 1: **Balance of benefits and harms of dexrazoxane treatment (vs no dexrazoxane) in children receiving anthracyclines**

Potential benefits and advantages*

- Clinical heart failure (8): lower risk in dexrazoxane group in most analyses (very low to low-quality evidence)
- Death resulting from heart failure (8): no significant difference (low-quality evidence)
- Clinical heart failure and subclinical myocardial dysfunction combined (8 and 6): lower risk in dexrazoxane group in most analyses (very low to low-quality evidence)
- Cardiovascular-related mortality (3): no significant difference (see other considerations; appendix p 28)

Potential harms and disadvantages*

- Overall survival and mortality (9): no significant difference (very low to low-quality evidence)
- Progression-free survival (8): lower risk in dexrazoxane group in some analyses, other analyses showed no significant difference (very low to low-quality evidence)
- Subsequent malignant neoplasms (8): possible higher risk in dexrazoxane group (very low to low-quality evidence)
- Subsequent malignant neoplasm related mortality (8): no significant difference (see other considerations; appendix p 28)
- Tumour response (6): no significant difference (very low to low-quality evidence)
- Other severe or life-threatening toxicities (6): results differed based on specific toxicity assessed
- Quality of life (4): no evidence

Conclusions

For a cumulative doxorubicin or equivalent dose of less than 250 mg/m²

- Are the anticipated beneficial effects large? Uncertain, because the absolute risk is lower compared with cumulative anthracycline dose ≥250 mg/m² and the evidence is mainly based on studies with a high cumulative anthracycline dose
- Are the anticipated harmful effects small? Uncertain, because there is a possible risk of subsequent malignant neoplasms
- Are the beneficial effects large relative to harmful effects? Uncertain

For a cumulative doxorubicin or equivalent dose of 250 mg/m² or higher

- Are the anticipated beneficial effects large? Probably yes, because the absolute risk of heart failure or myocardial dysfunction is high and the beneficial effect is based on studies with a high cumulative anthracycline dose
- Are the anticipated harmful effects small? Uncertain, because there is a possible risk of subsequent malignant neoplasms
- Are the beneficial effects large relative to harmful effects? Probably yes

*Based on a combination of evidence from adult and paediatric studies. Number reported after outcome indicates the importance of the outcome (where 1–3 stands for low importance, 4–6 for important, and 7–9 for critical; appendix p 5).

The beneficial effect of dexrazoxane on cardiac outcomes (eg, clinical heart failure only and clinical heart failure and myocardial dysfunction combined) is largely supported by RCTs in adults who received doses of anthracyclines exceeding 350 mg/m^2 [46]. The translatability of these results to children might be limited because of differences in developmental stage and body composition. Nevertheless, we believe that extrapolation of data from adult studies to children might be reasonable if assuming the pathophysiology of anthracycline-induced cardiotoxicity, and thus the potential beneficial effect of

dexrazoxane, might not differ between adults and children. Importantly, children treated with cumulative anthracycline doses of at least 250 mg/m^2 are established to have a high absolute risk of heart failure[47] and represent a population of patients who might benefit most from primary prevention. Unfortunately, the available evidence does not allow for an assessment of the efficacy of dexrazoxane in children treated with higher versus lower anthracycline doses. A prospective study[48] provided preliminary results on 173 childhood cancer patients who received doxorubicin with or without dexrazoxane, which suggest that the cardioprotective effects associated with dexrazoxane are more pronounced in individuals who received higher dose doxorubicin (≥250 mg/m^2, vs <250 mg/m^2).

Our panel also deliberated on the safety of dexrazoxane. Results on anti-tumour efficacy—that is, worse overall mortality or survival, tumour response, and progression-free survival—yielded no reasons for concern. However, consideration of the risk of subsequent malignant neoplasms was complex due to varying results and potential contributing factors. Although the best-case analysis of RCTs and non-randomised studies showed no significant difference between the treatment groups, the panel agreed that given the consequential severity of developing a subsequent malignant neoplasm, the risk required substantial consideration. As with cardiotoxicity, the available evidence did not allow for an investigation of an anthracycline dose-dependent risk of subsequent malignant neoplasms.

Nevertheless, the following data about the risk of subsequent malignant neoplasms associated with dexrazoxane are reassuring. First, in a subgroup of children with data on subsequent malignant neoplasms who participated in the pediatric RCTs, Chow and colleagues[49] showed no significant difference in SMN-related mortality; the median follow-up time of the overall study was 18.6 years. Subsequent malignant neoplasm is a known late effect (which can occur years after cancer treatment) of childhood cancer. Although the main risk factor for subsequent malignant neoplasms is exposure to radiotherapy, chemotherapy drugs have also been associated with subsequent malignant neoplasms[50]. The most prevalent subsequent malignant neoplasms in the dexrazoxane studies[25,27,42,43] were acute myeloid leukaemia and myelodysplastic syndrome, which can be related to treatment with topoisomerase inhibitors (eg, etoposide) and alkylating agents[50]. In the included studies, it was unclear whether patients treated with dexrazoxane and those treated without received an equal number of treatment cycles and whether this was accounted for in the determination of subsequent malignant neoplasm prevalence. The panel further believes that longer follow-up time in the studies evaluating subsequent malignant neoplasms will not result in more cases of acute myeloid leukaemia and

myelodysplastic syndrome, given the short latency time of subsequent malignant neoplasms (<3 years).50 In addition, the non-randomised study from Seif and colleagues[44] found that etoposide exposure was a significant predictor of subsequent acute myeloid leukaemia (odds ratio 2·36; 95% CI 1·48-3·79), independent of dexrazoxane exposure. Radiotherapy exposure might also partially explain the increased subsequent malignant neoplasm risk. In one of the included paediatric RCTs,[25] patients were exposed to high doses of cranial radiotherapy. In the dexrazoxane group, five of eight subsequent malignant neoplasm cases were brain tumours, compared with zero of three subsequent malignant neoplasm cases in the control group. Consequently, the possible effect of etoposide or radiotherapy (or synergistic effect with dexrazoxane) cannot fully be ruled out when evaluating the risk of subsequent malignant neoplasms.

The panel decided to consider the balance between the benefits and harms of dexrazoxane for two treatment groups: children who received high-dose (≥250 mg/m^2) cumulative doxorubicin or equivalent (an anthracycline dose that has been associated with a risk of heart failure that is 5·2–11·5 times the risk in child survivors who were not treated with anthracyclines[5,51,52,53]), and low-dose (<250 mg/m^2) cumulative doxorubicin or equivalent. These groups were based on the risk of heart failure in accordance with the IGHG cardiomyopathy surveillance guideline[47]. The panel concluded that for patients whose planned treatment includes a cumulative doxorubicin or equivalent dose of at least 250 mg/m^2, the benefits of dexrazoxane treatment probably outweigh the harms. The panel also considered that dexrazoxane is acceptable to key stakeholders (ie, health-care providers and methodologists) and feasible to implement. For patients with planned treatment including a cumulative doxorubicin or equivalent dose of lower than 250 mg/m^2, the balance between the potential benefits and harms was deemed uncertain (inconclusive evidence).

The panel's overall recommendations for dexrazoxane administration in childhood cancer patients, including its strength according to the GRADE methodology, are summarised in panel 2 (appendix p 6).

Panel 2: **Recommendations for prevention of anthracycline-induced myocardial dysfunction with dexrazoxane in children with cancer**

- No recommendation can be formulated for dexrazoxane administration in children who are expected to receive a cumulative doxorubicin or equivalent dose of lower than 250 mg/m², because there is currently insufficient evidence to determine whether the reduced risk of clinical heart failure and myocardial dysfunction outweighs the possible risk of secondary neoplasms
- Administration of dexrazoxane is reasonable in children who are expected to receive a cumulative doxorubicin or equivalent dose of at least 250 mg/m² (very low to low-quality evidence, moderate recommendation); the health-care provider should discuss the balance between harms and benefits of dexrazoxane with the patients and families, and the final decision should be guided by the medical knowledge of the health-care provider

DISCUSSION

We present international harmonised recommendations for dexrazoxane administration in children with cancer who are expected to receive anthracyclines as part of their treatment. Until now, little guidance has been available for health-care providers on the use of dexrazoxane. This guideline might help clinicians effectively care for these patients and facilitate shared decision making with patients and families regarding the use of dexrazoxane.

Children with cancer who are treated with anthracyclines have a dose-related risk of myocardial damage that might progress to heart failure[2-4] and can contribute to early mortality[8,9]. Besides secondary and tertiary prevention strategies that aim to slow the trajectory of asymptomatic to symptomatic myocardial damage, primary prevention is crucial for patients for whom alternate non-anthracycline-containing regimens are ineffective. Within this international guideline, we formulated a recommendation for considering dexrazoxane administration with every anthracycline dose in patients who are expected to receive at least 250 mg/m^2 doxorubicin or equivalent, which was supported by existing evidence and panel consensus, on the basis of GRADE methodology. We were unable to formulate recommendations for patients who are expected to receive lower than 250 mg/m^2 doxorubicin or equivalent because of insufficient evidence on the balance between potential benefits and harms.

Although this guideline refers generally to anthracyclines, the included RCTs in adults only used doxorubicin or epirubicin, and those in children used only doxorubicin. The non-randomised studies defined anthracyclines differently—ie, one versus multiple analogues combined (with or without including mitoxantrone, an anthraquinone). The effectiveness

of dexrazoxane in patients who are treated with mitoxantrone was a consideration in guideline formation, as it is also strongly associated with an increased risk of heart failure[2]. However, several factors prevented our panel from making a recommendation. First, there are no RCTs assessing the effect of dexrazoxane on mitoxantrone-induced cardiotoxicity in patients with cancer. Furthermore, evidence suggests that the underlying mechanism of doxorubicin-induced and mitoxantrone-induced cardiotoxicity might differ[54]. The toxicity reported in association with mitoxantrone appears to originate from alterations in cardiac energetic metabolism, and a role of topoisomerase receptors has not been established yet[54]. Nonetheless, the absence of RCTs and unclear role of topoisomerase challenges the potential beneficial effect of dexrazoxane in patients treated with mitoxantrone.

Radiotherapy exposure to the heart region is a well-established risk factor for myocardial dysfunction[3,5,51,53,55] and evidence suggests that a combination of radiotherapy involving the heart region and anthracyclines is even more harmful[56-58]. Regarding current guideline, this risk is especially relevant for patients who are expected to receive low to moderate anthracycline doses (<250 mg/m^2) supplemented by radiotherapy, and our panel considered whether this should be incorporated in the recommendations. However, there is no available evidence to suggest that children receiving both low to moderate anthracycline doses and radiotherapy exposing the heart would benefit more from dexrazoxane treatment than children receiving only anthracyclines. Furthermore, the proposed working mechanism of dexrazoxane does not interfere with the underlying mechanism of radiotherapy-induced myocardial dysfunction, which is mainly related to myocardial fibrosis[59,60]. Our panel concluded that the proposed recommendations on the administration of dexrazoxane apply to all children with cancer treated with anthracyclines, irrespective of radiotherapy exposing the heart.

A further consideration is that absence of evidence of an effect should not be confused with absence of an effect. When comparing small treatment groups, a non-significant result might be due to low statistical power. Also, low a priori risk of heart failure due to low cardiotoxic dose or short follow-up time might explain why none of the participants in two of the three paediatric studies that evaluated heart failure developed heart failure. These limitations are also applicable for the other outcomes of interest.

We recognise there are knowledge gaps regarding the effects of dexrazoxane in children treated with anthracyclines. The RCTs in children evaluated outcomes after a short period from cancer treatment, with the median follow-up time ranging from 2·7 to 13·0

years[21]. Longer follow-up time in future studies would provide greater insight into events that develop many years after treatment, including myocardial dysfunction, heart failure, and subsequent solid tumours. Low event rates might have also hampered statistical analysis of cancer treatment-related risk factors for subsequent malignant neoplasms in patients treated with dexrazoxane. Lastly, given the paucity of information on the cost-effectiveness of dexrazoxane use, we were not able to integrate the considerations about economic cost (eg, direct cost of the medication and indirect costs such as increased need for transfusions or febrile neutropenia) into our recommendations. Future studies could consider the use of advanced health-economic modelling to address this unmet challenge[61-63].

The strengths of this effort to formulate a guideline are the evidence-based methodology, including an extensive literature search, data quality assessment, and use of the GRADE framework, which enables transparent reporting of the process. Furthermore, the recommendations were harmonised by a multidisciplinary panel of experts from across Europe and North America. This guideline aims to improve health outcomes by assisting decision making about when to co-administer dexrazoxane with anthracycline treatment. We encourage future research to evaluate the efficacy of dexrazoxane in children receiving a doxorubicin or equivalent dose <250 mg/m^2, cardiac outcomes after long-term follow-up, risk factors associated with subsequent malignant neoplasms in children treated with anthracyclines and dexrazoxane, and the role of dexrazoxane in patients who are expected to receive mitoxantrone. Research should also investigate the clinical and genetic risk factors that can identify those who would benefit most from dexrazoxane, the beneficial effect of dexrazoxane on survival by reducing anthracycline-induced dose-limiting cardiotoxicity, and the variations in use of dexrazoxane in clinical practice, and the cost-effectiveness of dexrazoxane administration in children.

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SUPPLEMENTAL MATERIAL

A. Dexrazoxane cardioprotection guideline panel

B. Guideline development process

C. Search strategies

D. Inclusion criteria

E. Importance of outcomes

F. Grading system

G. Bibliography of included studies

H. Evidence tables

I. Summary of findings tables (including the GRADE assessment and detailed conclusions of evidence)

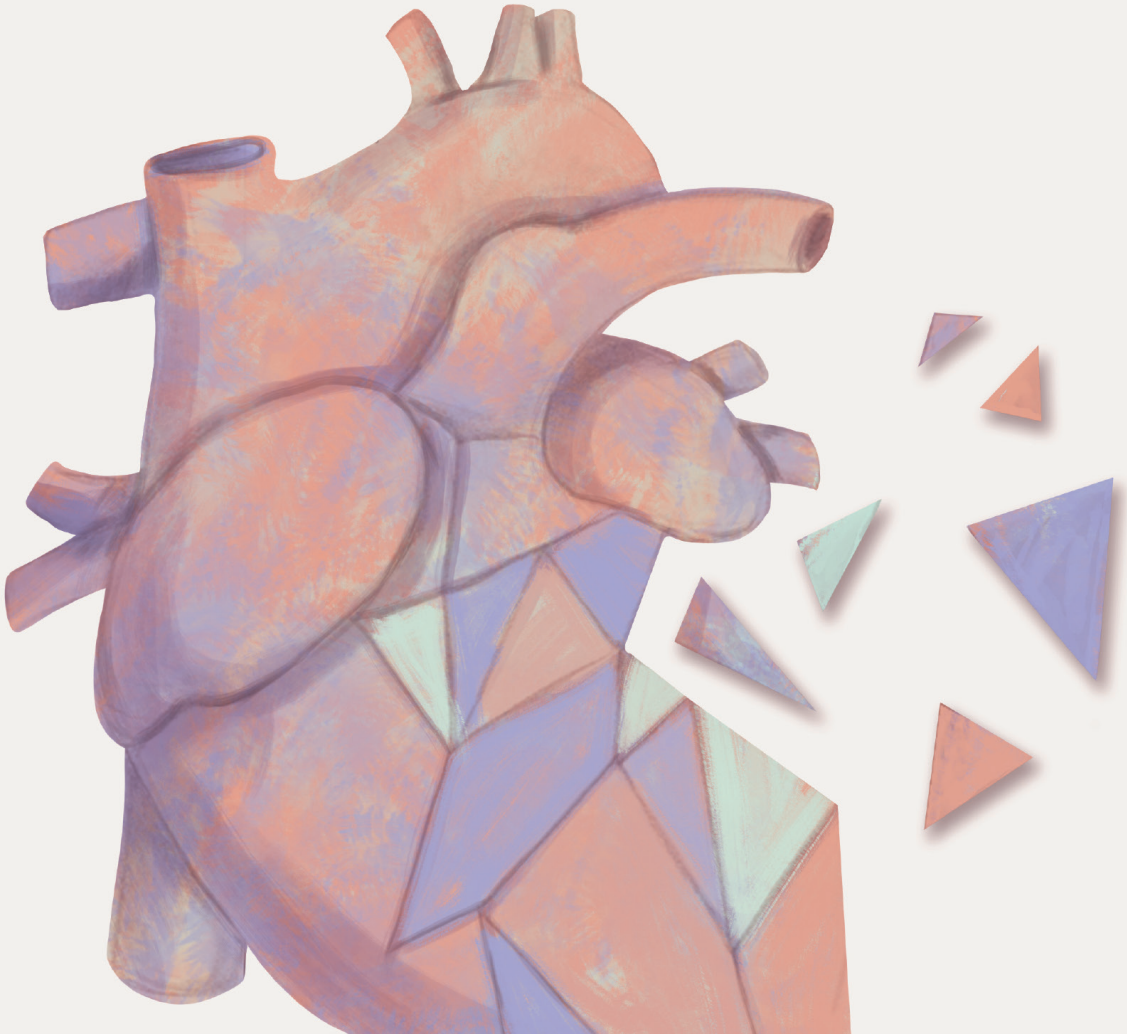
J. Overview of subsequent malignant neoplasm (SMN) cases and detailed information on primary diagnosis and treatment

K. Adverse effects other than cardiotoxicity and SMN

L. Evidence-to-Decision framework

M. Gaps in knowledge and directions for future research

The supplemental material of this study (appendix A to M) is not included in this thesis due to its extensive nature. It can be found online in: Lancet Child Adolesc Health. 2022 Dec;6(12):885-894. doi: 10.1016/S2352-4642(22)00239-5. Epub 2022 Sep 27.



CHAPTER 6

General discussion and future perspectives

Cardiac dysfunction is currently the most common non-cancer-related cause of mortality in survivors[1,2] and has a significant impact on quality of life. The general objectives of this theses were to assess the effect of low doses of cardiotoxic treatment on the risk of heart failure, to evaluate the role of ECG examination in cardiomyopathy surveillance of survivors and to develop an international guideline for the administration of dexrazoxane in children who are expected to receive anthracyclines.

Summary of main findings and general discussion

Risk stratification

The Pan-European cohort study in **Chapter 3** comprises ≥5-year childhood cancer survivors who were diagnosed between 1940 and 2009 in seven European countries. We investigated the cumulative incidence of symptomatic heart failure in 36,205 survivors. We identified survivors with heart failure as a first event by using multiple strategies, for example linkage to population-based databases and patient-based questionnaires. We defined heart failure according to the Common Terminology and Criteria for Adverse Events[3] grade 3, 4, and 5.

In our study, the cumulative incidence of heart failure was 2% (95% CI 1.7-2.2) by 50 years of attained age. We showed that the cumulative incidence of heart failure related mortality (grade 5) is lower for those treated in more recent decades, which is in line with other studies evaluating cardiac-related mortality[1,4]. Besides reductions in cardiotoxic cancer treatment dose, this could be explained by improvements in early detection and treatment of cardiac diseases resulting in less progress of disease. Developments in detections strategies could also explain why we found a higher cumulative incidence of heart failure (grade 3-5) in survivors who were treated in more recent periods (>1980). Other possible contributing factors are improved survival, an increase in protocols containing anthracyclines and more awareness among survivors and general practitioners for cardiac diseases after cancer treatment. A study evaluating self-reported heart failure in survivors from the United States showed opposite results[5]. We postulate that the difference in the degree of changes in treatment intensity[5,6] and the difference in era grouping could play a role. Nevertheless, both studies support continuous efforts to reduce the exposure to cardiotoxic cancer treatment.

In the case-control study in **Chapter 3**, we investigated the risk of heart failure after exposure to low doses of cardiotoxic cancer treatment and provided accurate dose-response evidence due to its high number of cases (n=500). Using phantom-based radiotherapy

(RT) reconstructions, our study showed a significant risk of heart failure in survivors who were exposed to a mean heart RT dose of 5-<15 Gray. Our results are of great clinical importance, especially given that previous guidelines could not make cardiomyopathy surveillance recommendations for survivors treated with prescribed chest RT<15 Gray (in the absence of anthracycline exposure) due to lack of evidence[7].

Regarding anthracyclines, our case-control study did not identify a significant increased risk of heart failure for survivors treated with <100 mg/m^2 cumulative anthracycline dose which is in line with previous studies[8-10]. In the light of cost-effectiveness[11], the recommended cardiomyopathy surveillance for this specific group should be reconsidered. Though, there were some cases with heart failure in this treatment group which could be explained by the presence of cardiovascular risk factors and genetic susceptibility to anthracycline-induced cardiomyopathy[8,9].

In our data we found no evidence of an effect modification by age at diagnosis regarding the roles of anthracyclines or heart RT on the risk of heart failure. This suggests that the association between cardiotoxic cancer treatment and heart failure exists across all age groups. However, risk of heart failure seems to increase with younger age at diagnosis[10].

Early detection

It is assumed that a certain degree of cancer treatment-induced cardiomyopathy is reversible and could be enhanced by prompt initiation of heart failure therapy[12]. Hence, early detection of myocardial dysfunction is warranted. ECG examination is a relative cheap, widely available and easy tool to assess the electrical function of the heart. Its role in cardiomyopathy surveillance is delineated in **Chapter 4**.

In **Chapter 4.1**, we systematically evaluated the prevalence of ECG abnormalities and the risk factors of ECG abnormalities in studies investigating ≥2-year childhood cancer survivors who were exposed to cardiotoxic cancer treatment. We performed a literature search within MEDLINE, EMBASE and CENTRAL (1966-11/2020) and reference lists of relevant studies. We found that various ECG abnormalities have been described in survivors years after cardiotoxic treatment and that large studies with clearly defined ECG abnormalities are sparse.

This gap in knowledge is addressed by the study described in **Chapter 4.2** by reporting the prevalence of ECG abnormalities according to the widely used Minnesota Code. For this study we used data from the Dutch Childhood Cancer Survivor Study LATER

cohort (1963-2001) part 2; clinical visit & questionnaire study. We included 1,381 ≥5-year childhood cancer survivors exposed to well-known (anthracyclines, mitoxantrone and/or heart RT) or potentially cardiotoxic cancer treatment (cyclophosphamide (intravenous), ifosfamide or vincristine without anthracyclines, mitoxantrone and/or heart RT), and sibling controls.

The prevalence of survivors with ECG abnormalities was calculated in all survivors and in each of the (potentially) cardiotoxic cancer treatment groups. Major ECG abnormalities were predominantly detected in survivors exposed to heart RT with or without anthracyclines (including mitoxantrone) (18-24%). This in line with results from the St. Jude Lifetime Study which reported a prevalence of 17-23% in childhood cancer survivors exposed to heart RT[13].

To identify ECG abnormalities associated with systolic dysfunction, we included survivors who received anthracyclines, mitoxantrone and/or heart RT, without a previous diagnosis of cardiomyopathy to reflect the surveillance population. Our results suggest that ECG abnormalities start to occur in survivors with more advanced myocardial dysfunction, hence, this diagnostic tool seems ineffective for early detection.

Besides detection of cardiomyopathy, diagnostic tools could also aid in the reduction of unnecessary echocardiograms during follow-up of survivors. ECG examination might be of value. We used the LASSO regression (least absolute shrinkage and selection operator) to select which of the predefined ECG abnormalities and continuous ECG measures were best discriminating between an abnormal and normal systolic function. We provided evidence that ECG examination contributes to ruling-out concurrent LVEF <45%, as adding “abnormal ECG based on LASSO analysis” and heart rate to a model (including well-known patient and cancer-treatment related risk factors) reduced the number of false positives with 49% (n=293). This strategy had a high sensitivity (93%), high negative predicted value (99%) and reasonable specificity (56%).

Currently, there is no consensus on the use of ECG in cardiomyopathy surveillance and the use of ECG will differ per institution. Our study is an important step towards establishing the value of ECG in the surveillance of cardiomyopathy in survivors. Before a diagnostic test or strategy (prediction model) can be recommended for use in clinical practice, it is essential to evaluate its performance by means of clinical validity and clinical utility. Decision curve analysis is an elegant way of assessing the clinical impact, because it can be applied without evidence on the impact of indirect test effects on health outcomes and costs which is normally required for decision analysis[14-17].

Primary cardioprotection

While the prescribed doses of anthracyclines have decreased over the past decades, a part of the children with cancer are still exposed to a doxorubicin or equivalent dose of >250 mg/m^2 which is associated with a high risk of future cardiomyopathy[7]. Primary cardioprotection with dexrazoxane is widely investigated, but clear guidance on the administrations in children is lacking[18-20]. In the updated Cochrane review (**Chapter 5.1**) we collected and summarized the available evidence form randomized controlled trials to investigate the efficacy and safety of dexrazoxane in both children and adults treated with anthracyclines. In parallel to this effort, a working group within the IGHG reviewed the existing literature and developed a guideline for dexrazoxane administration in children with cancer who are planned to receive anthracyclines by using evidence-based methodology (**Chapter 5.2**).

The updated Cochrane review included 13 studies (8 in adults, 5 in children) and showed that treatment with dexrazoxane results in less cardiotoxicity without influencing the anti-tumor efficacy. The meta-analysis of secondary malignant neoplasms (SMN) could not entirely eliminate the ongoing concerns due to varying results. However, as described in the IGHG guideline, these results should be interpreted in the light of the following aspects. Results from Chow et al. suggested no difference in SMN-related mortality between survivors who received dexrazoxane and those who did not after long-term follow-up[21]. In addition, the included participants were also exposed to other chemotherapeutic agents such as etoposide and high radiotherapy doses which are associated with an increased risk of SMNs[22,23]. After careful consideration of the data, their effect (or synergistic effect with dexrazoxane) could not fully be ruled out when evaluating the risk of SMN.

As the risk of cardiomyopathy increases with cumulative anthracycline dose, the expert panel concluded that the benefits likely outweigh the risk of subsequent neoplasms when the cumulative doxorubicin or equivalent dose is ≥250 mg/m^2 (moderate recommendation). No recommendation could be formulated for cumulative doxorubicin or equivalent doses of <250 mg/m^2.

For the clinical perspective it is interesting to realize that primary cardioprotection, may not only benefit cardiac outcomes during survivorship. Mitigating acute cardiotoxicity during cancer treatment could result in less anthracyclines dose modifications and thus improving cancer survival[24,25]. Consequently, there is great interest in strategies that alter distribution or clearance of anthracyclines in the myocardium. Although evidence in children is limited, studies showed promising effects of using longer infusion duration, liposomal

anthracyclines or a supervised exercise program during cancer treatment[26-28]. In addition, studies investigated whether timing of anthracycline administration (chronomodulated chemotherapy) potentially influence the tumor and cardiotoxicity response[29,30].

Methodological considerations

Risk stratification

In **Chapter 3**, the risk of bias was minimized by the method of data collection and heart failure ascertainment including extensive validation. This is a great advantage compared to the large multicenter studies that analyzed self-reported outcomes[31,32]. However, the different types of heart failure ascertainment used by the sub-cohorts might have introduced bias. Besides the advantages of linkage, there is a risk of missing a substantial part of cases[33] resulting in an underestimated cumulative incidence of heart failure.

It was deliberately chosen to include only heart failure and not asymptomatic myocardial dysfunction. Asymptomatic myocardial dysfunction would mainly have been identified through follow-up care and follow-up care is not organized in the same way among European countries. Furthermore, we fixed the final end-of follow-up date separately for each sub-cohort as the last date on which cardiac follow-up was available for ≥80% of sub-cohort-members. This was done to limit the effect of cardiac follow-up being available for survivors with heart failure and not for the survivors without heart failure.

Early detection

Even though we used a very broad search strategy for identifying eligible studies in **Chapter 4.1**, the presence of language bias cannot be completely ruled out in the systematic review. We included all studies reported in English and Dutch, but studies reported in other languages may have been missed.

For the cardiology project of the DCCSS LATER 2 there was a 54% response and may not be totally random. Females were slightly overrepresented in the cardiology project (48% of the participants versus 39% of the non-participants). In **Chapter 4.2** we adjusted the analysis for sex, but replication of our results is needed before conclusions can be drawn. Beyond the selection bias, it is a good sign that female survivors were willing to participate in studies evaluating cardiovascular diseases in order to expand the knowledge on the women's heart[34].

The risk of information bias was reduced by the following strategies. The data-managers who collected information on the survivors' characteristics and cancer treatment were

unaware of the outcome and the investigators who analyzed the outcome were unaware of the exposures. The participating survivors answered the questionnaires before the outcome assessment.

The risk of confounding was limited, as we performed multivariable regression including well-established risk factors of cardiomyopathy. Unmeasured factors such as genetic variations or transient cardiotoxicity during cancer treatment are unlikely to be strong confounding factors in the relationship between the investigated factors and the risk of ECG abnormalities. However, validation of our results remains an important part of future research as our analysis included few events.

Primary cardioprotection

The systematic review in **Chapter 5.1** used a very broad search strategy for identifying eligible studies. Thus, although it is unlikely that we missed eligible studies, it is never possible to completely rule out reporting and language bias. The results were based on studies from Europe, the United States, Canada and China. Although not all studies reported on every outcome, we assume that the overall conclusions are applicable for the average population in developed countries.

The strengths of the guideline in **Chapter 5.2** are the evidence-based methodology, including an extensive literature search, data quality assessment, and use of the GRADE framework, which enables transparent reporting of the process. The available evidence was of very-low to moderate quality and additional data was needed to translate the evidence into recommendations. Hence, with new studies becoming available, it is important to re-evaluate the guideline in the future.

Recommendations for future research

Risk stratification

- Evaluate the effect of low radiotherapy doses on the risk of heart failure in more recently treated survivors as radiotherapy techniques have changed tremendously in recent decades.
- Invest in an update of the online tool provided by Chow et al.[10] and consider additional predictors such as genetics, echocardiography, ECG and blood biomarkers.
- Evaluate with clinical trials whether it is safe to reduce the dose of anthracyclines, mitoxantrone or radiotherapy in treatment regimens or even omitting it.

Early detection

- Evaluate the association between ECG measures (such as QTc time and Q-waves) and future cardiac events to improve risk stratification.
- Evaluate fragmented QRS (fQRS) as this ECG pattern has been studied in different populations with cardiac diseases and results suggest that presence of fQRS reflects left ventricular conduction slowing caused by either scar, fibrosis, inflammation or ischemia[35]. A few studies investigated fQRS in cancer patients after therapy and showed that both cardiac radiation dose and anthracycline dose are associated with occurrence of fQRS[36-39].
- Investigate the clinical validity and utility of a diagnostic rule including ECG measures and blood biomarkers to rule-out concurrent myocardial dysfunction. These types of cohort studies including decision curve analysis are of great relevance to improve the cost-effectiveness of cardiomyopathy surveillance in survivors.

Primary cardioprotection

- Establish the long-term effects of dexrazoxane in survivors who participated in the RCTs and observational studies, as the follow-up time of current studies is relatively short.
- Investigate the efficacy and safety of dexrazoxane use in survivors treated with mitoxantrone. In some European and North American countries, the children who are diagnosed with acute myeloid leukemia receive dexrazoxane during mitoxantrone treatment. Collaborations should be initiated to evaluate the myocardial function of those treated with and without dexrazoxane.
- Investigate the efficacy and safety of other primary cardioprotection types such as liposomal anthracyclines, choronomodulated chemotherapy and physical exercise.

Recommendations for clinical practice - childhood cancer treatment

Risk stratification

- Collect mean heart radiotherapy dose during cancer treatment as it is of great clinical value for the cardiac follow-up of survivors.

Primary cardioprotection

- Consider and discuss the use of dexrazoxane when a patient is expected to receive a cumulative doxorubicin or equivalent dose of ≥250 mg/m^2.

Recommendations for clinical practice - follow-up of childhood cancer survivors

Risk stratification

- Recommend against follow-up or lessen the frequency for survivors who have a cumulative anthracycline dose of <100 mg/m^2 as only cardiotoxic risk factor.
- Implement mean heart radiotherapy dose in the cardiomyopathy surveillance guideline as this measure accurately reflects heart involvement and is becoming more and more available.
- Consider follow-up of survivors who received a mean heart RT dose of ≥5 Gray.

Early detection

- Be aware of ischemic ECG abnormalities (pathologic Q-waves and ST-T abnormalities) as these are more common in survivors, especially in those exposed to heart radiotherapy, than in the general population and severe cardiac ischemia can already occur at age <30 years.

Primary cardioprotection

- Continue with cardiomyopathy surveillance during survivorship according to the IGHG guideline.

Future perspectives

Multiple aspects of cardio-oncology need further exploration:

- The value of advanced echocardiographic measures and (novel) blood biomarkers in the risk stratification and early detection of cardiotoxicity in survivors.
- The sex differences in development and presentation of cardiotoxicity and responsiveness to cardiac medication.

- Risk stratification could be further improved by longitudinal measurements to update individual risk predictions, machine learning algorithms, genetics or detection of subtle markers during or early after cancer treatment.
- Effectiveness of lifestyle interventions as survivors have an increased risk to develop cardiovascular risk factors which are associated with cardiac disease.
- Guidance on the initiation and continuation of heart failure medication for both childhood cancer patients and survivors is warranted.
- The role of patients, parents and survivors in achieving translational research.

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NEDERLANDSE SAMENVATTING

In de afgelopen decennia is de overleving van kinderen met kanker aanzienlijk verbeterd. Helaas hebben survivors een sterk verhoogd risico op het ontwikkelen van late effecten als gevolg van de kankerbehandeling, waarvan hartschade één van de meest ernstige is. Hartschade wordt voornamelijk veroorzaakt door bepaalde type chemotherapie zoals anthracycline (doxorubicine, daunorubicine, idarubicine en epirubicine) en mitoxantrone, of als gevolg van radiotherapie waarbij het hartgebied betrokken is. We noemen deze type behandelingen ook wel cardiotoxische kankerbehandeling. Indien hartschade optreedt kunnen er verschillende hartziekten ontstaan, namelijk cardiale dysfunctie (=verminderde knijpkracht van het hart zonder symptomen), hartfalen (=verminderde knijpkracht van het hart met symptomen/overlijden), cardiale ischemie (=hartinfarct), pericarditis (=ontsteking van het hartzakje), hartklepaandoeningen en ritmestoornissen. Hartziekten zijn gerelateerd aan hogere cumulatieve doseringen van de cardiotoxische kankerbehandeling en hebben vaak progressief ziektebeloop.

Ongeveer de helft van de survivors is blootgesteld aan cardiotoxische kankerbehandeling. Tien procent daarvan zal binnen 40 jaar na de kankerdiagnose cardiale dysfunctie of hartfalen ontwikkelen. Hartfalen is momenteel de meest voorkomende niet-kanker gerelateerde oorzaak van sterfte bij survivors en heeft een duidelijke invloed op de kwaliteit van leven.

Cardio-oncologie is snel opgekomen als sub-specialisme van de cardiologie en het aantal publicaties op dit gebied is enorm toegenomen. Dit proefschrift omvat een overzicht van de huidige stand van zaken met betrekking tot hartziekten bij survivors van kinderkanker (**hoofdstuk 2**) en meerdere nationale en internationale studies die nieuwe inzichten opleveren met betrekking tot risicostratificatie (**hoofdstuk 3**), vroegtijdige opsporing (**hoofdstuk 4**) en primaire cardioprotectie (**hoofdstuk 5**) van cardiale dysfunctie en hartfalen.

Risicostratificatie

Onderzoeken hebben aangetoond dat hoge dosis cardiotoxische kankerbehandeling een verhoogd risico geeft op hartfalen, echter, was er nog weinig bekend over het risico van lagere doseringen. Hierdoor ontbraken aanbevelingen voor monitoring van cardiale dysfunctie en hartfalen voor bepaalde risicogroepen.

In **hoofdstuk 3** beschrijven wij een onderzoek waarin wij de prevalentie van hartfalen berekenen in een groot Europees cohort van meer dan 30.000 survivors van kinderkanker. Ons onderzoek liet zien dat 2% van alle survivors bij een leeftijd van 50 jaar de diagnose hartfalen heeft gekregen. Ook toonde het onderzoek aan dat sterfte door hartfalen lager is voor degenen die in recentere decennia zijn behandeld. Daarnaast hebben wij onderzocht of lage doseringen van bepaalde type chemotherapie en radiotherapie op het hart een verhoogd risico geven op hartfalen. In deze studie vonden wij nieuw bewijs dat survivors die een lage gemiddelde radiotherapie dosis op het hart hebben gekregen (5-<15 Gray), al een verhoogd risico op hartfalen hebben. Ook vonden wij geen significant verhoogd risico op hartfalen voor survivors die werden behandeld met een lage cumulatieve anthracycline dosis (<100 mg/m^2) in vergelijking met de survivors die geen anthracycline behandeling hebben gehad. Deze nieuwe bevindingen kunnen gevolgen hebben voor nieuwe behandelingsprotocollen voor kinderen met kanker en voor richtlijnen voor cardiale dysfunctie monitoring.

Vroegtijdige opsporing

Het is belangrijk om cardiale dysfunctie in een zo'n vroeg mogelijk stadium op te sporen zodat interventies mogelijk progressie naar hartfalen kunnen voorkomen. Op dit moment wordt de hartfunctie van survivors met een verhoogd risico eens per 2-5 jaar (afhankelijk van de cumulatieve dosis) beoordeeld middels echocardiografie en eenmalig middels ECG. Afhankelijk van deze resultaten wordt een survivor doorverwezen naar een cardioloog. Er is nog geen duidelijke consensus over de toegevoegde waarde van ECG-onderzoek bij survivors met een verhoogd risico op cardiale dysfunctie. In **hoofdstuk 4** onderzoeken wij de rol van ECG bij survivors met een verhoogd risico.

In **hoofdstuk 4.1** hebben wij een systematische review geschreven, dit is een verzameling en samenvatting van de al gepubliceerde studies over de prevalentie van ECG-afwijkingen en risicofactoren voor het ontwikkelen van ECG-afwijkingen bij survivors van kinderkanker. Deze systematische review liet zien dat er veel verschillende ECG-afwijkingen voorkomen waarvan een deel klinische gevolgen kan hebben voor survivors. Ook werd door deze studie zichtbaar dat er weinig studies zijn die helder gedefinieerde ECG-afwijkingen in grote cohorten hebben onderzocht.

In **hoofdstuk 4.2** berekenen wij de prevalentie van ECG-afwijkingen volgens de veelgebruikte Minnesota Code in een nationaal cohort. Voor deze studie gebruikten wij gegevens van de Nederlandse Childhood Cancer Survivor Study LATER cohort (1963-2001) deel 2; klinisch bezoek & vragenlijststudie. Wij includeerden 1.381 survivors die ≥5-jaar geleden zijn blootgesteld aan kankerbehandeling die (potentieel) schadelijk is voor het hart. Belangrijke ECG-afwijkingen werden voornamelijk gezien bij survivors die behandeld zijn met radiotherapie in het hartgebied, met of zonder anthracyclines. Onze resultaten suggereren dat bij een slechtere hartfunctie ook meer ECG-afwijkingen aanwezig zijn, daarom lijkt dit diagnostische hulpmiddel niet effectief voor vroege opsporing. Echter, toevoeging van bepaalde ECG-afwijkingen aan de huidige strategie kan van waarde zijn om klinisch relevante hartdysfunctie uit te sluiten. Hiermee kan het aantal echocardiografieën mogelijk verminderd worden. Toekomstig onderzoek is nodig om deze bevinding en de rol van ECG duidelijker te maken.

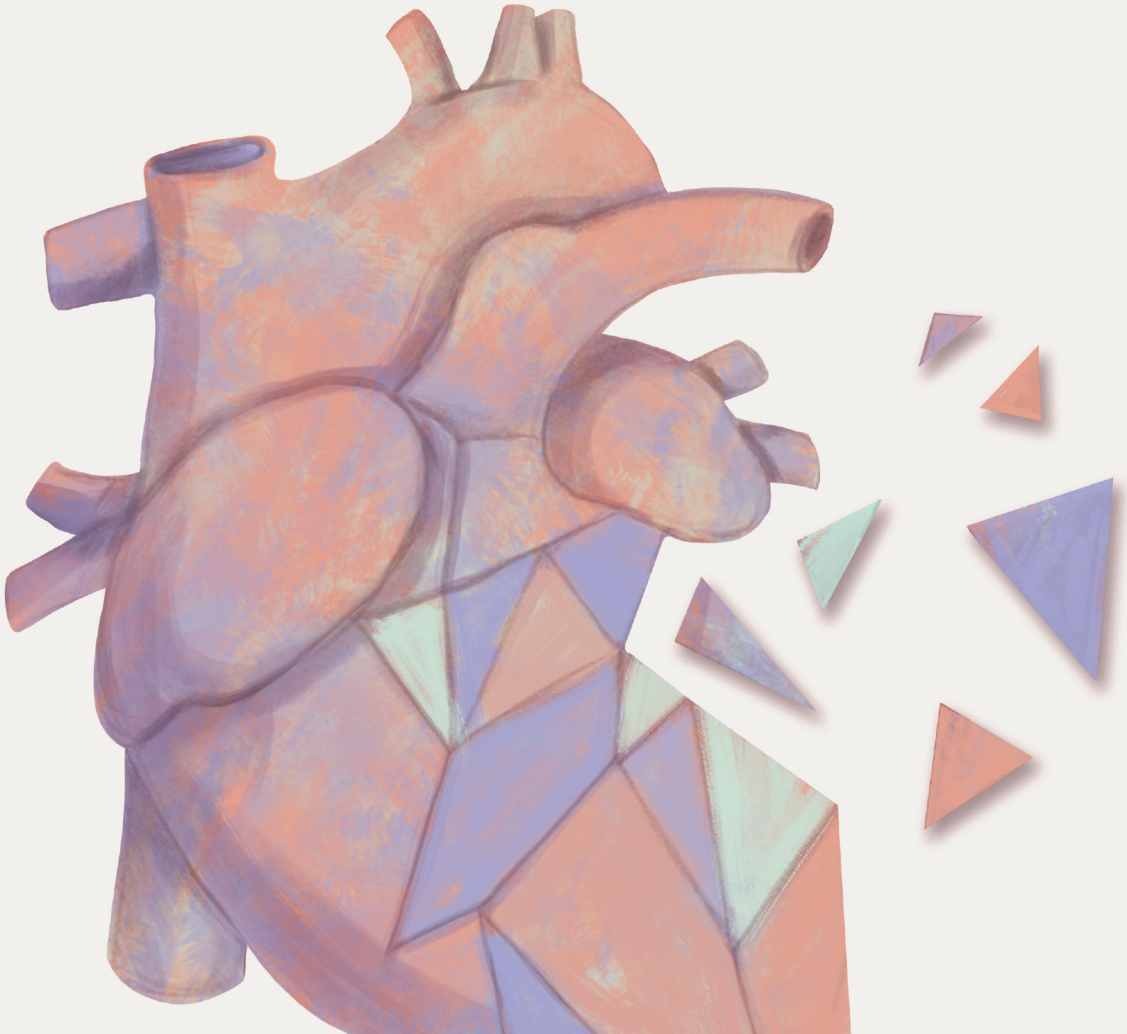
Primaire cardioprotectie

Naast het verlagen van de dosis en het vroegtijdig opsporen van hartschade is er ook steeds meer aandacht voor primaire preventie van cardiale dysfunctie als gevolg van anthracyclines. Dit is relevant omdat anthracyclines nog deel uitmaken van ongeveer de helft van de behandelrichtlijnen voor kinderkanker. Het hart beschermen met medicamenten, bijvoorbeeld dexrazoxane, is een van de mogelijkheden om hartschade als gevolg van anthracyclines te voorkomen dan wel verminderen. Dexrazoxane wordt sinds de jaren 80 gebruikt zonder dat er internationale richtlijnen zijn voor het gebruik bij kinderen.

Hoofdstuk 5.1 is een systematische review naar de effectiviteit en veiligheid van dexrazoxane bij kinderen en volwassenen die behandeld zijn met anthracyclines. Aangezien er geen internationale richtlijn bestond voor het gebruik van dexrazoxane bij kinderen hebben wij parellel aan hoofdstuk 5.1 de bestaande literatuur beoordeeld en in **hoofdstuk 5.2** een richtlijn ontwikkeld met een panel van 20 experts. Doordat er onvoldoende bewijs beschikbaar was hebben wij geen aanbeveling kunnen formuleren voor het gebruik van dexrazoxane bij kinderen die naar verwachting een lage tot matige dosering anthracyclines zullen krijgen. Voor kinderen die naar verwachting een hoge dosis anthracyclines zullen krijgen, raden wij aan om het gebruik van dexrazoxane te overwegen en de voor- en nadelen te bespreken met de patiënt en ouders.

Conclusies

De studies in dit proefschrift dragen bij aan de verbetering van de cardiale zorg voor zowel survivors als toekomstige kinderkanker patiënten. De studies hebben geleid tot een verbeterde identificatie van survivors met een verhoogd risico op hartfalen als gevolg van de kankerbehandeling, tot meer beschikbare kennis over de toepassing van ECG binnen cardiale dysfunctie monitoring en tot duidelijke handvaten voor het gebruik van dexrazoxane bij kinderen. Ook hebben wij met ons onderzoek hiaten in kennis geïdentificeerd die in de toekomst mogelijk een verschil kunnen maken voor de zorg aan survivors van kinderkanker.



APPENDICES

A

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LIST OF FREQUENTLY USED ABBREVIATIONS

CCS	childhood cancer survivors
Chest RT	chest-directed radiotherapy
ECG	electrocardiogram
Gy	Gray
Heart RT	heart-directed radiotherapy
HF	heart failure
IGHG	International Late Effects of Childhood Cancer Guideline Harmonization Group
LV	left ventricle
LVEF	left ventricular ejection fraction
RCT	randomized controlled trial
Survivor	childhood cancer survivor

LIST OF PUBLICATIONS

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Leerink JM, Feijen EAM, de Baat EC et al. Performance of a biomarker based diagnostic model for cardiac dysfunction in adult survivors of childhood cancer: A report from the Dutch Childhood Cancer Survivor Study. Submitted.

Merkx R, Leerink JM, Feijen EAM, de Baat EC, et al. Extensive Cardiac Function Analyses using Contemporary Echocardiography in Childhood Cancer Survivors. Submitted.

ABOUT THE AUTHOR

Esmée Christina de Baat was born on the 29th of September, 1994 in Raamsdonksveer, the Netherlands. After graduating from secondary school at the Mencia de Mendoza Lyceum in Breda in 2012, she continued to study medicine at the University of Utrecht. During her study she worked extra-curricular on a scientific paper about the role of imaging in cancer treatment induced cardiomyopathy at the department of Pediatric Cardiology, Wilhelmina Children's Hospital. This was her first step into this topic.

After completing medical school in 2019, she started her PhD program at the Princess Máxima Center in Utrecht, under the supervision of prof. dr. Leontien Kremer, prof. dr. Livia Kapusta, dr. Lieke Feijen and dr. Annelies Mavinkurve-Groothuis to study cardiotoxicity in childhood cancer survivors. Her PhD research resulted in this thesis. In 2022, she started as a pediatric resident (ANIOS) at Meander Medical Center in Amersfoort. Currently, she is working as internal medicine resident (ANIOS) at Antoni van Leeuwenhoek hospital in Amsterdam.

DANKWOORD

Op 1 maart 2019 startte mijn reis als promovenda en had ik het geluk om in een rijdende trein te kunnen stappen met prachtige onderzoeken en inspirerende mensen vol expertise over de late effecten van kinderkanker. Ik grijp dit moment dan ook graag aan om een aantal hiervan in het bijzonder te bedanken.

Allereerst wil ik de *survivors en hun families* bedanken voor deelname aan de studies en het beschikbaar stellen van gegevens voor wetenschappelijk onderzoek. Het is bewonderingswaardig hoe jullie je tijdens of na een ziekteperiode inzetten voor de gezondheid van anderen.

Hooggeachte leescommissie, *prof. dr. T. Leiner, prof. dr. M.M. van Noesel, prof. dr. A.H.E.M. Maas, dr. M.G. Slieker en prof. dr. H.M. Verkooijen:* Enorm bedankt voor het vrijmaken van uw tijd om dit proefschrift kritisch te beoordelen en zitting te nemen in de promotiecommissie.

Mijn promotieteam bestaat uit vier geweldige vrouwen die mij allemaal, elk op haar-eigen manier, inspireren. Dank voor jullie vertrouwen en alle kansen!

Prof. dr. L.C.M. Kremer, Leontien: wat een voorrecht om in jouw onderzoeksgroep te mogen werken. Vanaf moment één was het voor mij duidelijk hoe bevlogen, enthousiast, kundig en doelgericht jij je inzet voor meer kennis over de lange termijneffecten van kinderkanker. Ik heb ontzettend veel geleerd van onder andere onze schrijf-sessies via zoom; jij kunt data als geen ander vertalen naar de kliniek en dat ook nog eens krachtig overbrengen op papier. Dank voor je overzicht, belangrijke feedback en persoonlijke touch!

Prof. dr. L. Kapusta, Livia: ondanks jouw ontzettend drukke baan als kindercardioloog in Tel Aviv, was je altijd betrokken en op de hoogte. Tijdens onze gezamenlijke LATER-CARD meetings was je kritisch maar wist jij ook te zorgen voor empowerment en gevoel van trots op wat we hadden bereikt. Dank voor jouw visie op de berg aan data over het hart, je snelle feedback en gedrevenheid!

Dr. E.A.M. Feijen, Lieke: jij hebt mij wegwijs gemaakt in de wereld van de wetenschap; van meetings plannen tot het presenteren op congressen en alles daartussenin. Door jouw geduld en toegankelijkheid heb ik nooit een drempel gevoeld om hulp te vragen en je had ook nog eens altijd een oplossing voor me klaar. Ik ben jaloers hoe jij zonder te knipperen de methodologie van iedere studie op weet te rakelen. Dank voor het delen van jouw kennis, kijk op het leven, (brandweervrouw) anekdotes en gezelligheid!

Dr. A.M.C. Mavinkurvé-Groothuis, Annelies: door jouw positieve energie, daadkracht en flexibiliteit heb ik met veel plezier met je samengewerkt. Hoewel we verschillende type projecten onder onze hoede hadden, was er altijd een rode draad, namelijk die ene vraag "wat kan ik voor je doen?". Na een overleg met jou was alles weer zo licht als een veertje en kon ik verder met concrete mogelijkheden. Dank voor de motiverende gesprekken over de studies en mijn toekomst en het inkijkje in jouw invulling van het artsenvak!

Ook heel hartelijk dank aan alle coauteurs en andere betrokkenen voor jullie bijdrage aan de papers. Ik wil de volgende collega's in het bijzonder noemen:

Wouter: voor alle uren die je geïnvesteerd hebt in het verzamelen van de ECG-data, het uitpluizen van de literatuur en de gedetailleerde feedback op de papers. *Elvira*: voor het delen van je kennis, precisie en doorzettingsvermogen tijdens het werken aan de systematic reviews. *Renée*: voor het vertrouwen in mij als coördinator, voor je richtlijnexpertise, scherpe pen en pragmatische aanpak. *Jacqueline, Heleen & Saskia:* voor jullie ideeën en waardevolle feedback. *Margriet (& centraal bureau LATER):* voor de prachtige dataset. *Maria en Jos*: voor jullie ondersteuning. *ProCardio & PanCareSurFup people, Saro and Melissa:* many thanks for the collaborations, working with you was inspiring and I have learned a lot from you.

En last but not least, de andere twee minions. *Jan*: toen jij al op het vliegveld van Philadelphia na een congres je laptop openklapte om verder te werken aan je R-script wist ik het zeker, die wordt belangrijk voor de statistiek! *Remy*: jouw frisse en nuchtere blik vanuit het oosten was een heerlijke toevoeging aan alle discussies. Dank voor jullie bijdrage aan de papers, behulpzaamheid, toegankelijkheid en bovenal gezelligheid!

Van het knusse kantoor op de tweede afgewisseld met de Rode Luifel, naar thuiswerken, naar de balzaal op de vierde: wat was het leuk om met jullie, *Rebecca* de onuitputbare kletser, *Kim* de vrolijke zonnestraal, *Yuehan* the dedicated explorer, *Lisanne* de rust zelve, *Jikke* de bezige-bij en *Jop* de epi&quizmaster en alle andere lieve collega's uit TEAM LATER, deze intensieve tijd samen te beleven. Heel veel dank voor alle gezellige koffies en wandelingen, "het even meekijken" voor nieuwe inzichten, de vrijdagquizzen, jullie interesse, de chocola en receptentips en de super blije appjes voor en na mijlpalen!

Heyn, Tim, Jesse, Arco en Willeke: dankzij jullie werd het zaadje cardiotoxiciteit bij mij gepland en door jullie aandacht is het sindsdien flink gaan groeien. Bedankt dat ik mijn eerste stappen als wetenschapper onder jullie vleugels heb mogen zetten!

Collega's van het Meander MC: dank voor de fijne samenwerking!

Lieve *vriendinnen (Floor, Frouk, Juul, Fee, Herten, Jekergirls, Saar, JC Pièrre, Roos, San, Lou, San) en (schoon-)familie:* jullie gezelligheid, de etentjes, de vakanties naar binnen- en buitenland, de coronahobby's, de concerten, de fanatieke hockeywedstrijden, de feestjes, het uren kletsen over helemaal niks, de kaft van dit proefschrift al bedenken voordat ik überhaupt was begonnen, jullie humor, oprechte interesse en reflectie op wat we meemaken, hebben stuk voor stuk bijgedragen aan deze reis. Ik ga naar jullie toe met een glimlach en kom met een nog grotere glimlach terug. Ik ben jullie ontzettend dankbaar! En in het bijzonder lieve *Leo en Puck*, het is een enorm cadeau om jullie naast me te hebben staan als mijn paranimfen.

Lieve *de Baatjes;* het warme, sportieve, ietwat competitieve en gezelligste nest, dank voor jullie onvoorwaardelijke support. Voor mij zijn jullie de beste!

Pap, ik weet zeker dat jij de enige bent die mijn artikelen inclusief gemarkeerde zinnen op zijn nachtkastje heeft liggen, en wat maakt dat me trots. *Mam*, hoeveel minuten zullen wij al niet gebeld hebben? Gewoon om bij te kletsen, mij door de autorit na mijn nachtdienst heen te helpen of omdat ik je advies nodig heb (Es, gewoon doen!). Ik bewonder hoe jullie met volle overgave en enthousiasme dingen aanpakken. Jullie hebben mij geleerd om alles uit jezelf te halen, een duidelijk plan te hebben, te zorgen voor genoeg leuke dingen en, niet onbelangrijk, te sporten. De discipline en het doorzettingsvermogen dat ik af en toe nodig had voor dit proefschrift, heb ik zeker weten van jullie!

Steef en Max; wie als eerste de titel van mijn proefschrift kan herhalen..!! Nee hoor grapje, jullie gezonde portie geheugenverlies houdt mij gelukkig wakker voor al het andere in het leven. Ik ben apetrots op hoe jullie in het leven staan en heb nu alweer zin om te huilen van het lachen met jullie!

Lieve *Jep*, ze zeggen wel eens dat het laatste jaar van je PhD het zwaarste is, maar het tegenovergesteld is me overkomen, want jij kwam halverwege aan boord. Je was mijn klankbord en fungeerde als boksbal iedere keer als ik dit nodig had, je geeft me vertrouwen, de ruimte en een duwtje als dat nodig is en bovenal voelt het altijd als thuiskomen en één groot feest om met jou te zijn. Ik kijk uit naar de toekomst samen met jou!