Cardiovascular late effects in adult survivors of childhood cancer

Brouwer, C.A.J.

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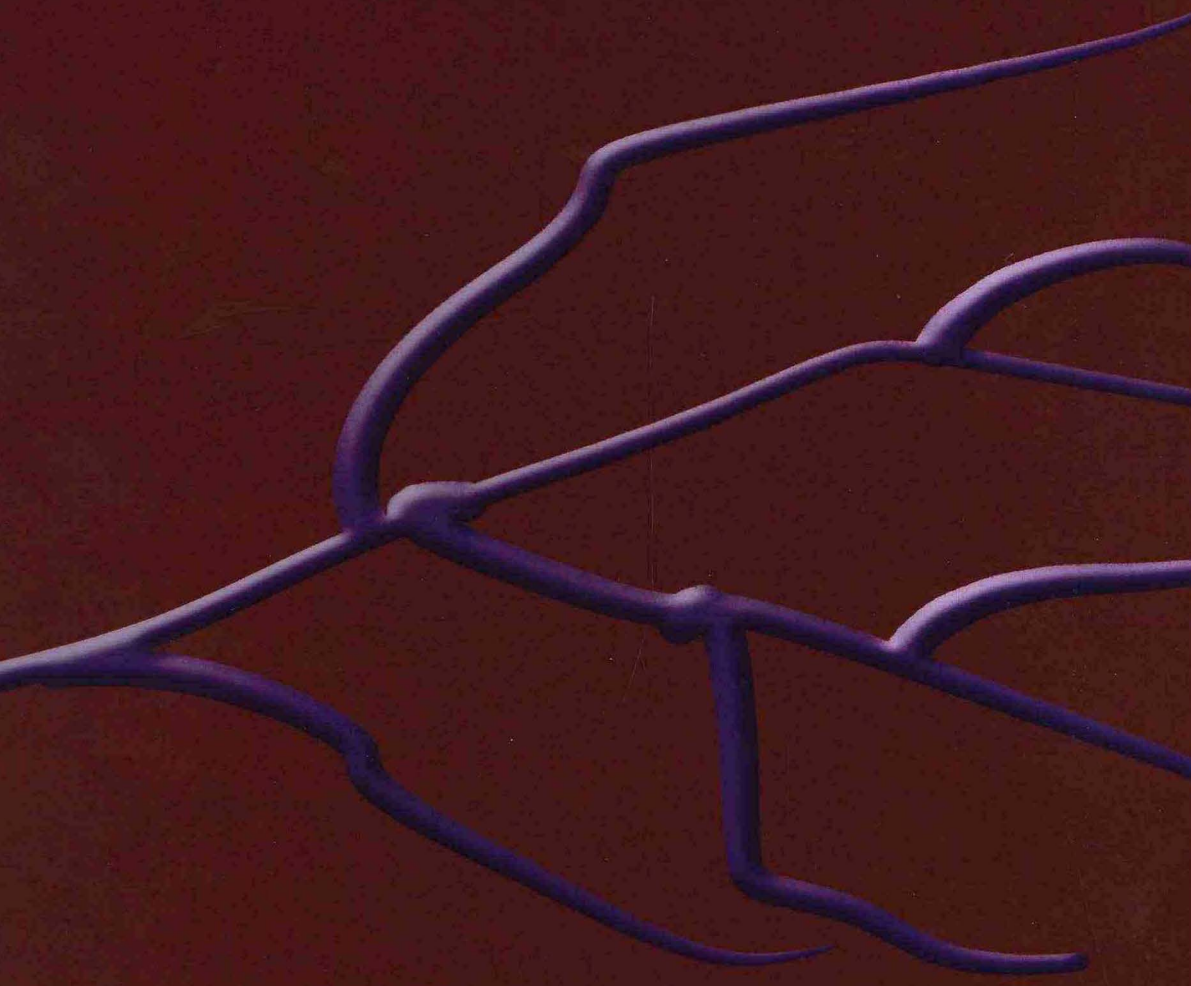

Inge Brouwer

Cardiovascular Late Effects in Adult Survivors of Childhood Cancer

Stellingen behorende bij het proefschrift

"Cardiovascular Late Effects in Adult Survivors of Childhood Cancer"

Inge Brouwer

1. Lifelong (cardiac) follow-up is warranted in anthracycline-treated childhood cancer survivors.
   This thesis.

2. In long-term childhood cancer survivors treated with potentially cardiovascular-toxic cancer treatment, the risk of underweight after reaching final height is increased in those who received high dose anthracyclines.
   This thesis.

3. Treatment with anthracyclines, chest irradiation or both treatment modalities in childhood is associated with a risk of diastolic dysfunction in adulthood.
   This thesis.

4. Irradiation in childhood is associated with a higher risk of endothelial dysfunction and an unfavorable cardiovascular risk profile in adulthood.
   This thesis.

5. Determination of NT-pro-BNP and/or troponin is not contributory in the detection of subclinical cardiac damage in long-term survivors of childhood cancer.
   This thesis.

6. Until now, diastolic dysfunction in childhood cancer survivors is a prognostic mystery.

7. Creation of uniformity in the submission process of manuscripts still remains a pious hope.

8. Research is solving one problem and creating several new ones.

9. You can't manage time, but you can manage the way in which you consume your time.
   "Winnie-the Pooh on Success"

10. Learning without thought is labour lost; thought without learning is perilous.
    Confucius (551-479 v. C.)

11. The beginning of all science is the astonishment on how things are as they seem to be.
    Aristoteles (384-322 v.C.)

The printing of this thesis was financially supported by Stichting Kinderoncologie Groningen (SKOG), Stichting Werkgroep Interne Oncologie, Groningen University Institute for Drug Exploration (GUIDE), and Pfizer bv. and Novartis Pharma bv.

The studies described in this thesis were supported by a grant of the foundation "The Quality of Life Gala 2003".

ISBN: 978-90-367-3622-0
ISBN electronic version: 978-90-367-3623-7

Page lay-out: P. van der Sijde, Groningen, the Netherlands
Design of the cover: Joline en Tineke Brouwer
Printed by: van Denderen B.V., Groningen, the Netherlands

RIJKSUNIVERSITEIT GRONINGEN

Cardiovascular Late Effects in Adult Survivors of Childhood Cancer

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 10 december 2008
om 13.15 uur

door

Cornelia Alberdina Johanna Brouwer

geboren op 4 augustus 1978
te Rheden

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Voor papa & mama

Paranimfen:	Eryn Liem Carianne L 'Abée

TABLE OF CONTENTS

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

In the last decades, survival in childhood cancer showed an enormous increase[1-4]. Children diagnosed before 1950 were treated predominantly with surgery and radiotherapy, while those treated afterwards received combination treatments with more extensive use of chemotherapeutic agents. Studies performed in Europe showed that children diagnosed with cancer in the 90s had an overall 5-year survival between 70-75%[2-4], while in the 60s the overall 5-year survival was less than 25% [3]. Also in the United Stated (US) survival rates increased significantly: children with cancer diagnosed between 1975-1977 had an overall 5-year survival of 62%, while overall 5-year survival in those diagnosed between 1996-2002 was 80%[5]. The increase in survival during the last decades can be largely attributed to improvements in cancer treatment and supportive care.

During the first years after completion of cancer treatment, survivors receive regular follow-up visits. The main purpose of these follow-up visits is early detection of a relapse. With prolonged disease-free survival the risk of a (late) relapse declines. However, the prevalence of late complications related to previous cancer treatment increases. Screening of long-term survivors shows a wide variation of possible late complications, such as endocrine deficiencies, cardiovascular disease, and secondary tumors[6-10]. A study in 1362 long-term survivors of childhood cancer with a median follow-up of 17 years showed that 75% of the survivors had one or more late effect and 40% had at least one severe or life-threatening or disabling adverse effect[10]. The highest burden of disease due to late effects was seen after previous radiotherapy treatment (55% treated with 'radiotherapy only' had a high or severe burden of events, compared with 15% and 25% among survivors treated with 'chemotherapy only' and 'surgery only', respectively)[10]. In addition, survivors with a more extensive follow-up (> 20 years after childhood cancer diagnosis) had more severe late effects compared with those diagnosed more recently (follow-up < 20 years post-treatment)[11]. In the University Medical Center Groningen, follow-up of childhood cancer survivors has been organized in a dedicated clinic at the Department of Pediatric Oncology. With increasing follow-up the childhood cancer survivors reach adult age, which underlines the necessity of cooperation with a broad variety of specialists (i.e. specialists of the Departments of Internal Medicine, Medical Oncology, Endocrinology, Cardiology, etcetera, and with the general practitioners of the survivors).

Cardiovascular disease and associated risk factors

A population-based study about mortality in childhood cancer survivors showed that five or more years after completion of cancer treatment cardiac disease is one of the most important causes of death (survivors are 8.2 times more likely to die because of cardiac disease compared with a US reference population)[12]. Clinical and subclinical cardiotoxicity in childhood cancer survivors has been known since three decades[13-15]. Anthracyclines

and chest irradiation have been identified as treatment-related risk factors in late-onset cardiotoxicity, especially when given in combination with each other and/or in higher dosages[16]. Thus far, cardiac function was mainly studied by echocardiography and by parameters of systolic function. Only a few studies assessed diastolic function; however, these studies were performed in small cohorts of survivors and by means of load-dependent echocardiography parameters[17-19]. The importance of analyzing subclinical diastolic dysfunction has been established by studies in the general population, that showed that subclinical diastolic dysfunction may proceed to clinical (diastolic) heart failure, even in the absence of systolic dysfunction[20,21]. In addition, it is important to assess diastolic and systolic cardiac function by means of load-independent parameters, i.e. independent of left ventricle filling, thereby causing less intra-and inter-individual variance in the interpretation of cardiac results. Furthermore, knowledge on the prevalence and underlying mechanisms of subclinical systolic and diastolic dysfunction is essential in order to develop measures to prevent progression to clinical heart failure.

Besides an increased prevalence of cardiac events, also vascular events have been described as more prevalent in childhood cancer survivors compared with controls [7,22,23]. Late-onset stroke was assessed by Bowers et al[22,23] in a large ongoing multi-center study in adult survivors of childhood cancer. Compared with sibling controls, an increased risk of stroke was found in survivors of childhood leukemia (treated with or without cranial radiotherapy; relative risk (RR) 6.4; 95% confidence interval (CI) 3.0-13.8) and brain tumor (with/without cranial-RT; RR 29.0; 95% CI 13.8-60.7)[22]. Also survivors of childhood Hodgkin disease, treated with mantle field irradiation, had an increased risk of stroke (RR 5.6; 95% CI 2.6-12.3)[23]. The prevalence of subclinical vascular damage, i.e. premature atherosclerosis, is hardly known in childhood cancer survivors. Premature atherosclerotic changes of the carotid artery, as expressed by an increased intima media thickness, have shown to be directly associated with the development of cardiovascular events, such as stroke or myocardial infarction[24]. A study in adult testicular cancer patients before and shortly after completion of cisplatin-based chemotherapy showed an increased intima media thickness of the common carotid artery as compared with intima media thickness before cancer treatment[25]. Heikens et al investigated risk factors for cardiovascular disease in survivors of childhood brain tumor treated with cranial irradiation (≥25 Gy; mean follow-up 16 years post-treatment) and found an increased intima media thickness in the carotid bulb compared with controls [26]. In addition, survivors treated with neck irradiation were found to have an increased intima media thickness of the carotid artery[27].

In the general population, several cardiovascular risk factors, such as hypertension, dyslipidemia and obesity, have been found in the (progression of) development of

cardiovascular disease. In studies performed in survivors of adult cancer it has been shown that long-term survivors are at risk to develop cardiovascular risk factors at a younger age than expected in the general population[28,29]. Also in survivors of childhood cancer an increased prevalence of cardiovascular risk factors was found[26,30]. Oeffinger et al studied the cardiovascular risk factors in 26 survivors of childhood acute lymphoblastic leukemia treated with (n = 10) or without (n = 16) cranial irradiation[30]. They found that 16/26 (62%) survivors had at least one cardiovascular risk factor, while no difference in prevalence of risk factors was found between survivors treated with or without cranial irradiation [30]. The most common risk factors in childhood cancer survivors were obesity and dyslipidemia [30]. An increased prevalence of overweight/ obesity is found in survivors treated with cranial/ craniospinal irradiation[30-33]. On the other hand childhood cancer survivors treated with alkylating agents, anthracyclines, abdominal irradiation and/or total body irradiation were found to have an increased risk to develop underweight[34]. In the general population, both overweight (body mass index (BMI) ≥ 25 kg/m^2) and underweight (BMI < 20.5 kg/m^2) are associated with an increased all-cause mortality[35]. As most studies on evaluation of body composition in long-term childhood cancer survivors had a cross-sectional design, it is not possible to assess timing and the underlying mechanisms in the development of an abnormal body composition. Therefore, data on longitudinal changes of body composition are needed in survivors treated with radiotherapy and/or chemotherapy.

Aim of the thesis

The aim of this thesis is to assess the prevalence of clinical and subclinical cardiovascular disease and associated cardiovascular risk factors in childhood cancer survivors treated with potentially cardiovascular-toxic treatment, i.e. anthracyclines, platin-derivates and/ or radiotherapy.

Outline of the thesis

In **chapter 2** an overview of the literature with regard to changes in body composition in childhood cancer survivors is presented. Underlying mechanisms in the development of obesity are addressed, in order to discuss intervention strategies. To clarify the timing and the treatment-related risk factors in the development of under- or overweight after childhood cancer treatment, the results of a longitudinal study on BMI are presented in **chapter 3**. First, the prevalence of under- and overweight after reaching final height is assessed in 377 childhood cancer survivors 5 years or more after completion of potentially cardiovascular-toxic anti-cancer treatment (i.e. anthracyclines, platin-derivates and/ or radiotherapy). By multiple regression analysis, the association between under- and overweight at final height and the previous cancer treatment is studied. Finally, the annual BMI change from completion of cancer treatment until reaching final height in association

with previous cancer treatment is assessed by multilevel regression analysis.

Most published data on subclinical and clinical cardiac damage after childhood cancer treatment have been derived from cross-sectional or longitudinal studies with a medium follow-up up to 17 years. In chapter 4 and 5, the results of two longitudinal cardiac assessments in very long-term survivors are presented. The first study (presented in **chapter 4**) is performed in 22 survivors of a malignant bone tumor who received treatment with median to high doses of the anthracycline-derivate doxorubicin (≥ 225 mg/m^2). Median follow-up is 22 years. The results of echocardiography (systolic and diastolic parameters) and 24-h electrocardiograph (ECG; assessing heart rate variability as an indicator of autonomic cardiac function) are compared with those of two earlier cardiac assessments.

The second longitudinal cardiac study (presented in **chapter 5**) is performed in 23 survivors of childhood acute lymphoblastic leukemia who received 100 mg/m^2 of the anthracycline-derivate daunorubicin (n = 13) or no anthracyclines at all (n = 10). At median 22 years post-treatment, results of echocardiography and 24-h ECG are compared with measurements performed at median 12 years post-treatment in the same survivors.

In **chapter 6** the results of a cross-sectional cardiac assessment (i.e. echocardiography, ECG, baroreflex sensitivity measurement, and determination of N-terminal pro-brain natriuretic peptide) are presented. Two hundred seventy-seven childhood cancer survivors treated with anthracyclines, platin-derivates and/or radiotherapy and 130 age- and sex-matched sibling controls were included. If survivors received both doxorubicin and daunorubicin as part of their cancer treatment, the cumulative doses of doxorubicin and daunorubicin are added as they were considered equal in toxicity.

Little is known about subclinical vascular damage in childhood cancer survivors and studies performed thus far only concerned survivors who received cranial- and/or neck-irradiation. In the current study, dynamic and biochemical vascular function is assessed in 277 childhood cancer survivors who received several combinations of cancer treatment and in 130 sibling controls. Results are presented in **chapter 7**. The used methods are (1) intima media thickness of the carotid and femoral arteries; (2) flow-mediated dilatation of the brachial artery; (3) endothelial- and inflammatory marker proteins, such as Von Willebrand factor, high-sensitivity C-reactive protein, tissue-type plasminogen activator and plasminogen activator inhibitor type 1; (4) several cardiovascular risk factors, such as hypertension, hypercholesterolemia, metabolic syndrome, and renal dysfunction. Early signs of vascular damage and cardiovascular risk factors are investigated at median 18 years after completion of cancer treatment.

In **chapter 8**, the results of the studies in this thesis are summarized and discussed, and recommendations for further study are given. In **chapter 9,** this thesis is summarized in Dutch.

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CHAPTER 2

Changes in body composition after childhood cancer treatment: Impact on future health status – A review

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Critical Reviews in Oncology/Hematology 2007 July;63(1):32-46.

ABSTRACT

Purpose. To describe data on changes in body composition in childhood cancer survivors. Underlying mechanisms in development of obesity are addressed, in order to discuss intervention strategies.

Methods. A systematic literature search was undertaken with a number of search terms.

Results. Female survivors of ALL and brain tumours, especially if treated with cranial irradiation, showed a higher prevalence of obesity compared with the general population, while survivors of other malignancies had a higher prevalence of underweight. Influences of corticosteroid treatment and cytostatics on body composition are uncertain. Diminished physical activity, early adiposity rebound (<5 years of age) and/or hypothalamic involvement of tumour or treatment, and subsequent growth hormone deficiency, may play a role in the development of obesity in childhood cancer survivors.

Conclusion. Longitudinal prospective studies in more extensive cohorts are necessary to estimate actual prevalence and facilitate the unravelling of the underlying mechanisms in change of body composition.

ARTICLE OUTLINE

1. Introduction
2. Background of obesity
3. Methods in analysis of body composition
   - 3.1. Body mass index
   - 3.2. Dual energy X-ray absorptiometry
   - 3.3. Bioelectrical impedance analysis
   - 3.4. Air-displacement plethysmography
   - 3.5. Other methods for measurement of body composition
4. Results of analysis of body composition in childhood cancer survivors
   - 4.1. General prevalence of abnormal body composition in childhood cancer survivors
   - 4.2. Prevalence of abnormal body composition in relation to diagnosis
   - 4.3. Effect of cranial irradiation on body composition in childhood cancer survivors
   - 4.4. Effect of chemotherapy on body composition in childhood cancer survivors
   - 4.5. Timing in change of body composition after childhood cancer treatment
5. Underlying mechanisms of change in body composition in childhood cancer survivors
   - 5.1. Disturbed energy balance during and after childhood cancer treatment
   - 5.2. Hypothalamic damage after earlier childhood cancer (treatment)
   - 5.3. Gonadal dysfunction after earlier childhood cancer treatment
   - 5.4. Leptin resistance and genetic factors in development of abnormal body composition
6. Discussion
7. Conclusion

References

1. INTRODUCTION

In the general population, the prevalence of obesity increased substantially over the last few decades. Even in childhood obesity becomes an increasing problem. Studies in the United States (U.S.) reported a 3-fold increase in prevalence of childhood obesity compared with 40 years ago[1]. A recent study in U.S.-children aged 2–19 years, showed an increase in prevalence of overweight from 1999 to 2004 (respectively, 14% and 17%; $p < 0.05$)[2]. In The Netherlands, the prevalence of childhood overweight increased 2-fold and that of obesity 3-fold compared to 1980[3].

General health is threatened by obesity, especially in conjunction with other risk factors such as diabetes mellitus type II, hypertension and dyslipidaemia. It can eventually give rise to cardiovascular disease[4]. Prevention of obesity is an important issue and it may be even more important in cancer survivors who received potential cardiotoxic chemotherapy or radiotherapy and who are, because of their earlier treatment, prone to develop cardiovascular disease.

The main objective of this review is to describe data on changes in body composition after earlier treatment for childhood cancer. Furthermore, four secondary objectives were formulated. Firstly, what is the prevalence of abnormal body composition in childhood cancer survivors? Secondly, which cancer treatments affect body composition and which patients are at risk for obesity? Thirdly, what is the timing of changes in body composition? Finally, which mechanisms may be important in development of obesity, i.e. which intervention strategies can be used to prevent obesity, in order to preserve somatic and psychosocial health?

To address the above-mentioned objectives we performed Medline and Pubmed searches. We used the following MeSH terms: 'childhood cancer survivors', 'obesity', 'radiotherapy', 'chemotherapy', 'body composition', 'body mass index', 'dual energy X-ray absorptiometry', 'bioelectrical impedance analysis', 'energy intake', 'adiposity rebound', 'physical activity', 'growth hormone deficiency', 'gonadal dysfunction', 'gene polymorphisms'. We only included published data, written in English and only studies that investigated body composition in persons who were diagnosed for cancer under the age of 21 years.

2. BACKGROUND OF OBESITY

Childhood obesity appears to be an important factor in the development of overweight or obesity in adulthood[5]. Cheung et al[6] performed a longitudinal study in 12,327 persons in the general population and measured body mass index (BMI) at various moments in childhood and adulthood. They showed that BMI values at ages 11 and 16 years were

predictive for development of adult overweight and obesity as well as diabetes and hypertension[6]. In the general population, overweight or obesity earlier in life (aged 31–64 years) are independent risk factors for cardiovascular disease in older age (>65 years)[4]. An increased BMI in childhood was associated with increased common carotid artery intima media thickness (IMT) in adulthood (measurements at age 24–39 years)[7]. Increased IMT is a marker of subclinical atherosclerosis and predicts the likelihood of cardiovascular events in population groups[8,9].

Proposed factors, contributing to changes in body composition during and after treatment of childhood cancer, are multiple. Firstly, cancer treatment may induce metabolic changes, that affect body composition. For example, corticosteroid treatment may induce metabolic disturbances (for example hormonal deficiencies induced by suppression of the hypothalamic–pituitary–adrenal axis) during and after cessation of treatment and seems to be associated with obesity[10]. Furthermore, cranial irradiation (CRT) may induce development of obesity, probably because of damage to the hypothalamic–pituitary axis[11]. Children surviving brain tumours are at risk for development of obesity especially after more than 51 Gy irradiation to the hypothalamus[12]. Location of primary tumour might be another factor affecting body composition. Survivors of childhood craniopharyngioma had an about 50% increased rate of obesity[13]. Especially hypothalamic involvement had a major impact on change in body composition[13]. Survivors of hypothalamic or intrasellar tumours had significantly higher percentage (%) total body fat and abdominal fat compared with BMI-matched healthy controls[14]. Finally, disturbed energy intake and/ or physical inactivity in childhood cancer survivors might be factors in change in body composition. Reduced physical activity, rather than increased total energy intake, was found to be a major etiologic factor in the development of obesity in survivors of childhood craniopharyngioma[15]. In addition, low physical activity was a likely cause in development of obesity in CRT-treated ALL-survivors, who had an adequate caloric intake[16]. In contrast, Link et al[17] found no abnormal degree of physical exercise in 44 CRT-treated ALL-survivors compared with healthy controls.

Metabolic disturbances after childhood cancer treatment may eventually play a role in the development of the metabolic syndrome. The metabolic syndrome includes a range of cardiovascular risk factors, such as altered lipid profile, hypertension, impaired fasting glucose and obesity, described by an increased waist circumference (men >102 cm; women >88 cm). A combination of three or more risk factors indicates presence of the metabolic syndrome according to the National Cholesterol Education Program (NCEP) criteria[18]. Talvensaari et al [19] studied 50 survivors of several childhood malignancies (with exception of childhood brain tumour survivors) and 50 age-matched controls for

signs of metabolic syndrome. Eight of the 50 survivors (16%) had the triad of obesity, hyperinsulinaemia and low HDL cholesterol concentrations, compared with none of the controls ($P = .01$). Furthermore, survivors of childhood cancer had higher plasma glucose and insulin concentrations, lower HDL cholesterol levels and increased relative weight and body fat mass compared with controls. So, these survivors appeared to have an increased risk of the metabolic syndrome[19]. Of 15 survivors of craniopharyngioma, who had surgery in all cases and adjuvant radiotherapy in one, all had significantly increased abdominal adiposity, higher fasting triglycerides and lower HDL-cholesterol/total cholesterol ratio compared with BMI-matched controls. So, after surgery for craniopharyngioma, more features of the metabolic syndrome were present compared with controls, probably as a result of hypothalamic damage[14]. In contrast, Kourti et al[20] studied the metabolic syndrome in ALL-survivors treated with only chemotherapy and found that only three of the 52 survivors (5.8%) fulfilled criteria for the metabolic syndrome, which was not different compared with the general U.S. population. Also, Gurney et al[21] studied prevalence of metabolic syndrome in 75 long-term ALL-survivors (treated with or without CRT; mean 25 years post-diagnosis) and found no difference in prevalence of metabolic syndrome between survivors and controls.

Several studies indicated a higher prevalence of obesity in childhood cancer survivors. Obesity needs to be addressed in relation to the metabolic syndrome and subsequently to cardiovascular disease. This is especially important in childhood cancer survivors, who frequently are already at risk for cardiovascular disease due to earlier cardiotoxic cancer treatment.

3. METHODS IN ANALYSIS OF BODY COMPOSITION

3.1. Body mass index

Measurement of body composition in childhood cancer survivors can be performed by several methods. BMI is a world-wide used tool to measure overweight and obesity. Standardised measurements of weight and height (by anthropometry) are necessary for calculation of BMI. BMI is calculated by the formula: weight (kg)/height^2 (m). Janssen et al[22] studied BMI in 14,924 adult persons and found that BMI is a significant predictor of metabolic health risk. For every 1.0 kg/m^2 increase in BMI odds of metabolic syndrome increased by 15%[22]. Formulation of cut-off points for BMI in childhood are based on international data and linked to the widely accepted adult cut-off points for overweight and obesity, e.g. 25 and 30 kg/m^2 [23]. Use of BMI for assessment of body composition creates the possibility for childhood cancer survivors to measure their own heights and weights in order to calculate BMI. Investigators of the Childhood Cancer Survivor Study (CCSS) used this method by sending questionnaires to childhood cancer survivors and

to sibling controls. In this way it became possible to calculate BMI in an extensive cohort of survivors[24]. However, changes in BMI are not always related to changes in %body fat, especially not in elderly people and in people who have relatively high volume of lean body mass (e.g. in people who practise bodybuilding).

3.2. Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DEXA) is frequently used as measurement of body composition. DEXA measurement differentiates body weight into three compartments: lean soft tissue, fat soft tissue and bone (three-compartimental model). It can distinguish regional as well as whole body parameters of body composition. DEXA provides precise body composition analysis with a low radiation exposure[25]. Boot et al[26] studied body composition by DEXA in children and adolescents (aged 4–20 years) and found that %body fat, fat mass, lean tissue mass and bone mineral content correlated significantly with BMI. However, others found that %body fat values associated with BMI classifications of overweight and obesity vary considerably with age in growing children, especially in girls[27]. In conclusion, combination of several methods in measuring body composition, such as BMI and DEXA, seems to be necessary for reliable measurements, while prognostic relevance of DEXA alone is not yet established.

3.3. Bioelectrical impedance analysis

A non-invasive, simple to use and well tolerated method for measurement of body composition is bioelectrical impedance analysis (BIA). Measurement of total body impedance is the vector sum of resistance and reactance in the limbs and the torso (two-compartimental model). Lean tissue contains large amounts of water and electrolytes, which causes low resistance electrical pathway. On the other hand, fat and bone have high resistance electrical pathway, because they have low amounts of fluid and electrolytes. The limbs, because of the smaller circumference and greater length, contribute to most of the impedance. BIA measurements allow an estimation of total body water, but rely on a constant hydration state[28]. Fat mass and fat free mass (in kg) were determined by several equations, in order to calculate percentages from body weight. When electrode protocols are followed, BIA is the most reproducible technique in assessment of body composition: no differences were found among resistance values determined on 5 successive days[29]. Pecoraro et al[30] concluded that BIA was more accurate in measuring %fat mass than BMI. However, others stated that care must be taken in the choice of predictive regression equations used for the calculation of total body water and fat free mass, while they found significantly different outcomes in regression equations between two analysers of BIA[28]. A validation study of BIA with DEXA in American children showed that impedance measurements by BIA had a strong correlation with fat free mass determined by DEXA[31].

Until now, BIA was used less frequently compared with BMI and DEXA for determination of body composition in childhood cancer survivors[17,28,32,33]. Data on prognostic significance of BIA in measuring body composition are not available but need further investigation. BIA in combination with other techniques seem to be reliable in measuring body composition[31].

3.4. Air-displacement plethysmography

Besides BIA and DEXA, a new technique for measurement of body composition was evaluated in childhood cancer survivors: air-displacement plethysmography (BOD POD system). BIA uses a two-component model for measurement of body composition and DEXA a three-component model, while BOD POD divides the body into four components (four-component model): fat mass, water, protein and mineral. As formulated by Murphy et al[34], BOD POD combines the measurements of weight, body volume, total body water and bone mineral content. Fat-free mass is calculated as the difference between weight and fat mass. Dempster and Aitkens[35] stated that the test procedure of the BOD POD system is quick and convenient requiring minimal compliance. Furthermore, it appears suitable for persons at various ages and for persons of all weights.

Measurement of body composition in childhood cancer survivors by this new technique is only used so far by Murphy et al[34]. They described body composition by BOD POD in 24 childhood ALL-survivors and in 24 age-matched healthy controls. The ALL-survivors had been treated previously with either prednisolone (n = 15) or dexamethasone (n = 9) and with either 6-mercaptopurine or 6-thioguanine. Time since completion of treatment ranged from 1 to 2 years. They found that fat mass index (fat mass adjusted for body stature) was higher in survivors compared with controls (6.2 ± 4.1, respectively, 4.3 ± 1.4 kg/m^2, $P < .05$), but no significant differences between survivors and controls were found in %fat mass and fat mass. Furthermore, no differences in body composition were found between patients treated with prednisolone and patients treated with dexamethasone. However, the size of the cohort was very small and post-treatment follow-up short. In the future, air-displacement plethysmography may turn out to be an important technique in determination of body composition in childhood cancer survivors. Before introduction of this technique in clinical practice more extensive cohorts of survivors with a longer follow-up post-treatment have to be investigated. Furthermore, comparison with, i.e. BIA and DEXA is necessary. For none of these techniques predictive values are available.

3.5. Other methods for measurement of body composition

In combination with BMI some authors also measure waist-to-hip ratio in childhood cancer survivors. Especially waist circumference (classification of intra-abdominal fat) is

an important parameter in describing adiposity. A study on 14,924 adult persons showed that waist circumference alone is a strong positive predictor of co-morbidity. For every 1.0 cm increase in waist circumference, odds of metabolic syndrome increased by 6%[22]. In a recent study in Dutch children a strong correlation between waist circumference and BMI was found[36]. Furthermore, it was shown that a waist circumference above 1.3 standard deviation allows a reasonable approximation of overweight as defined according the international BMI cut-off values. Finally, Neville et al[37] studied waist:height ratio in childhood cancer survivors and found that this ratio emerged as a more important risk factor for metabolic abnormalities than BMI. A waist:height ratio >0.5 (defined as abdominal adiposity) was associated with a tendency to dyslipidaemia in pre-pubertal survivors and with raised insulinaemia and unfavourable lipid profiles in pubertal and adult survivors. The authors suggest that a waist:height ratio >0.5 might be an early and simple clinical marker for metabolic disturbances in the future[37].
Finally, measurement of skinfold thickness represents a simple method for assessment of body fat. Unfortunately, it's inter-observer variation is very high[38], which makes it less appropriate for routine clinical use.

4. RESULTS OF ANALYSIS OF BODY COMPOSITION IN CHILDHOOD CANCER SURVIVORS

The relationship between earlier cancer treatment and body composition has been studied by several authors. These studies mainly focussed on treatment modality and can roughly be divided into two main categories of treatment. The first category of treatment is CRT, mainly used in treatment of acute lymphoblastic leukaemia (ALL) and brain tumours. The second category of treatment is corticosteroid therapy, as part of polychemotherapy, mainly studied in ALL-survivors. Until now, as far as we know, the effect of chemotherapy combinations on body composition in childhood cancer survivors was only described by the CCSS [24].

Analyses of body composition in long-term childhood cancer survivors were mostly performed in cross-sectional studies or longitudinal studies in a retrospective cohort. Longitudinal prospective studies on body composition in survivors of childhood cancer are scarce[32,39,40]. Most of these studies concern small cohorts of survivors[32] and were performed during treatment and not thereafter [39]. However, Dalton et al [40] performed a prolonged prospective evaluation of anthropometric characteristics in an extended cohort of ALL-survivors. They studied weight, height and BMI at diagnosis and every 6 months thereafter until median 7.2 (range: 1.9–14.3) years post-treatment.

Most studies investigating body composition in childhood cancer survivors deal with

small numbers of patients and describe only the number of survivors with increased body weight parameters. As far as we know, underweight in childhood cancer survivors was only studied in the CCSS. This large multi-institutional study was performed in childhood cancer survivors, who survived 5 years or more after diagnosis for cancer. Late effects of earlier cancer treatment were registered by detailed questionnaires that were completed by 14,370 (70%) survivors of childhood cancer. Among other things, these long-term survivors registered their heights and weights for calculation of BMI. The described prevalences of overweight and underweight in these survivors will be summarised in Sections 4.1 and 4.2[24].

4.1. General prevalence of abnormal body composition in childhood cancer survivors

It is hardly possible to give an overall estimation of the prevalence of abnormal body composition in the entire group of childhood cancer survivors. Distinction should be made between several treatment modalities and childhood cancer diagnoses. Because of the large number of subjects, the results of the CCSS seem to be most indicative for a reliable assessment of prevalence of abnormal body composition in the entire group of childhood cancer survivors. They performed a cross-sectional analysis of BMI in 7195 (50%) survivors of several paediatric malignancies (5 years or more post-diagnosis) and showed lower prevalence of obesity in childhood cancer survivors compared to healthy controls (in females, respectively, 13% versus 17% and in males, respectively, 12% versus 17%) and higher prevalence of underweight in childhood cancer survivors (in female survivors 9% versus 5% in female controls and in male survivors 4% versus 1% of male controls) [24].

4.2. Prevalence of abnormal body composition in relation to diagnosis

Thus far, the CCSS-study on BMI in an extended cohort of survivors of several childhood malignancies has been the only study on body composition in survivors treated with multiple drug chemotherapy and/or radiotherapy. In this study the prevalence of abnormal body composition in relation to earlier cancer treatment and to cancer diagnosis could be estimated. As mentioned before, Meacham et al [24] found that survivors of most cancer types were more likely to be underweight compared to healthy controls (Table 1). Especially male survivors of childhood malignancies had higher prevalence of underweight compared to controls, mainly if they were diagnosed before the age of 4 years (odds ratio 12.4; $P = .001$). Only ALL-survivors treated with CRT ≥20 Gy had an increased risk of obesity in the CCSS-study (Table 1). An earlier study by CCSS that was performed in ALL-survivors only ($n = 1765$), showed that increased risk for being obese was especially present in female survivors with age at diagnosis 0–4 years (odds ratio 3.81; $P < .001$)[41]. A CCSS-study in 921 brain tumour survivors, found that female brain tumour survivors had

a 3-fold increased risk for being obese if the age at diagnosis was 9 years or less compared with those diagnosed at older ages ($P = .02$)[11]. Unfortunately, no information was given on the precise duration of follow-up, except that all participants survived 5 years or more post-diagnosis, restricting proper interpretation of the weight change after treatment.
Abnormal body composition, especially overweight and obesity, was also studied in smaller cohorts by other authors[10,38,42-45]. Recent literature is summarised in Table 1. According to these studies prevalence of obesity in ALL-survivors shows a wide variation and may be up to 47%.

4.3. Effect of cranial irradiation on body composition in childhood cancer survivors

Results of CCSS showed that the prevalence of obesity was increased in male and female childhood cancer survivors treated with CRT (odds ratios, respectively, 1.3 ($P = .02$) and 1.9 ($P < .001$); Table 2)[24]. Effect of CRT on body composition in childhood cancer survivors was also studied in smaller cohorts, with conflicting results (Table 2). Some of them showed no more obesity (measured by BMI; follow-up 4–18 years post-treatment)[10,46-48], while others, in accordance with the CCSS, found increased BMI in CRT-treated survivors compared with non-CRT-treated survivors[38,43-45] or compared with healthy controls[17]. Follow-up in these studies was up to 20 years. Some authors showed an increased BMI in male and female CRT-treated survivors[17,43,45], whereas others found an increased BMI only in females[38] or in males[44]. Moreover, Sklar et al[45] found a greater increase in BMI in survivors treated with 24 Gy CRT compared with those treated with 18 Gy ($P < .005$).

In the context of CCSS, Gurney et al[11] studied BMI in 921 brain tumour survivors and showed that treatment with surgery and CRT increased the risk of obesity in female survivors about 3-fold compared with surgery alone ($P = .005$). Others found that CRT-treated brain tumour survivors (n = 89) had similar BMI compared to those treated without CRT (n = 59). However, survivors who received ≥51 Gy CRT, especially if administered hypothalamic, had greater BMI increase compared to those who received less (Table 2). They concluded that hypothalamic damage, due to either tumour, surgery or CRT, is a regiospecific and primary risk factor for development of obesity in childhood brain tumour survivors. Another risk factor for BMI increase was younger age at diagnosis, independent of hypothalamic involvement[12].

In some studies in childhood cancer survivors DEXA was used as a more contemporary method for measurement of body composition (Table 2). Almost all DEXA-studies concern ALL-survivors. Results of these DEXA-studies showed higher %fat if survivors were treated with CRT[17,38,43,44,46,47], even if CRT-treated and non-CRT-treated survivors had similar BMI[46,47]. Only Nysom et al[48] found equal %fat at DEXA in CRT-treated and non-CRT-treated survivors

Table 1. Prevalence of abnormal BMI in childhood cancer survivors

	Number of ALL survivors	Prevalence of underweight in ALL survivors (BMI <18.5 kg/m^2)	Prevalence of overweight in ALL survivors			Prevalence of obesity in ALL survivors		Prevalence of abnormal BMI in survivors of other malignancies	Time of measurement post-treatment
			BMI ≥ p85	BMI 25-29.9 kg/m^2	BMI ≥25 kg/m^2	BMI >p90	BMI ≥30 kg/m^2		
Meacham et al [24]	1665	- Females: 4.2% (vs. 4.7% in controls) - Males: 3.5% (vs. 0.9% in controls)	--	- Females: 22.5% (vs. 23.4% in controls) - Males: 36.2% (vs. 42.8% in controls)	--	--	- Females: 18.5% (vs. 16.5% of controls) - Males: 16.5% (vs. 16.7% of controls)	-Male survivors of several childhood malignancies: increased risk of underweight -Female survivors of HD, WT, bone tumours: at risk for being underweight -Female brain tumour: at risk for obesity: 17.1% (vs. 16.5% of controls)	≥5 y post-diagnosis
Dongen-Melman et al [10]	113	--	--	--	--	-At cessation of treatment in dexamethasone-treated survivors: 43% -Survivors treated with combination prednisolone and dexamethasone (4y post-treatment): 44%	--	--	≤4 y post-treatment

Didi et al [42]	114	--	- 45% of males - 47% of females	--	--	--	--	--	At achievement of final height: for males and females respectively, median 8.4 y and 6.9 y post-treatment
Sklar et al [45]	126	--	- Overall prevalence: 30% - In patients treated without CRT: 10.5% - In patients treated with CRT (18 Gy, respectively, 24 Gy): 40%, respectively, 38%	--	--	--	--	--	At achievement of final height
Van Beek et al [43]	90	--	--	23/90 (26%)	--	--	In 7/90 (8%) of survivors	--	Mean FU: 12.7 (2.0-29.7) y post-diagnosis
Warner et al [38]	35	--	--	--	In 46% of survivors (vs. 22% in controls)	--	In 23% of survivors (vs. 6% in controls)	In survivors of several other childhood malignancies: * Overweight: 24% * Obesity: 5%	Mean FU: 6.6 (3.3) y post-treatment
Jarfelt et al [44]	35	--	--	12/35 (34%)	--	--	0/35 (0%)	--	Median FU: 20 y (minimum: 15 y)

Note: *, *P*-value based on comparison to healthy controls; ALL, Acute Lymphoblastic Leukemia; HD, Hodgkin disease; WT, Wilms' tumor; FU, follow-up; y, years; CRT, cranial irradiation; vs., versus

Table 2 Effect of cranial irradiation (CRT) on body composition in childhood cancer survivors

	Number of survivors (treated with CRT; type of childhood malignancy)	Dose CI	Differences in BMI between CRT-treated survivors vs. non-CRT-treated survivors or controls	%Fat mass, measured by DEXA, between CRT-treated survivors vs. non-CRT-treated survivors or controls	Follow-up duration
Meacham et al [24]	7195 (2147; several malignancies)	Unknown	-Female CRT-treated: OR for being obese (BMI ≥ 30 kg/m^2) was 1.9 (vs. controls, $P < .001$) -Male CRT-treated: OR for being obese was 1.3 (vs. controls, $P = .02$)	--	≥ 5 y post-diagnosis
Dalton et al [40]	618 (445; ALL)	18 Gy	If age at diagnosis <13 y → significant increase in BMI *z*-scores, regardless whether they received CRT	--	93/618 reached final height: median 7.2 (1.9-14.3) y post-diagnosis
Dongen-Melman et al [10]	113 (52; ALL)	18-25 Gy	No differences	--	Up to 4 y post-treatment
Nysom et al [47]	95 (39;ALL)	15-24 Gy	No differences	Increased %fat in survivors treated with CRT (vs. controls; $P < .05$)	Median 7.6 (1.2-18.3) y post-treatment
Brennan et al [46]	32 (32; ALL)	18-25 Gy,	No differences ($P = .10$)	Higher in survivors (vs. controls; $P < .05$)	Median 17.8 (6.8-28.6) y post-treatment
Van Beek et al [43]	90 (19; ALL)	Unknown	CRT-treated had higher BMI (vs. controls; $P < .01$)	Higher in CRT-treated survivors (vs. non-CRT-treated survivors; $P < .01$)	Mean 12.7 (2.0-29.7) y post-diagnosis
Link et al [17]	44 (44; ALL)	18-30 Gy	Higher BMI in CRT-treated (vs. age- and sex-matched controls; $P = .005$)	CRT-treated survivors had higher fat mass compared to controls ($P = .002$)	Median 16.7 (6.3-23.9) y post-treatment
Warner et al [38]	35 (35; ALL)	18-24 Gy	BMI *z*-score was higher in CRT-treated female ALL-survivors (vs. non-CRT-treated female survivors of other malignancies or controls; $P < .01$)	Higher in female ALL-survivors (vs. female survivors of other malignancies or female controls; $P < .01$)	Mean 6.6 (±3.3) y post-treatment
Jarfelt et al [44]	35 (19; ALL)	18-24Gy	Higher BMI in CRT-treated men (vs. non-CRT-treated men; $P = .002$)	Higher in CRT-treated men (vs. non-CRT-treated men; $P = .001$)	Median 20 y

Sklar et al [45]	126 (88; ALL)	18 Gy (n=35) 24 Gy (n=53)	-During treatment, significant change in BMI SDS in CRT-treated ($P < .001$), while no significant change in non-CRT-treated -BMI SDS change in CRT-treated survivors: most pronounced in 24Gy-treated survivors (vs. 18 Gy-treated ones; $P < .005$)	---	At attainment of final height:
Nysom et al [48]	46 (6; malignant lymphoma)	Median 24 Gy	No differences	No differences ($P = .11$)	Median 8.7 (1.4-24.5) y post-treatment
Gurney et al [11]	921 (656; brain malignancy)	<20 Gy (n=85) 20-39 Gy (n=58) 40-59 Gy (n=389) ≥60 Gy (n=34) unknown (n=90)	-If treated with CRT, OR of 1.84 for having a BMI ≥ 30 kg/m^2 ($P = .02$), especially in female CRT-treated survivors (OR 2.96; $P = .005$). -Radiation dose between 40-59 Gy: higher risk for being obese ($P = .005$), especially in females	--	≥5 y post-diagnosis
Lustig et al [12]	148 (89; brain cancer)	<51 Gy (n=23) 51-55Gy (n=46) >55Gy (n=20)	-CRT ≥ 51 Gy → greater BMI change (vs. CRT-treatment < 51 Gy; $P = .002$)	--	Up to 140 months

Note: CRT, cranial irradiation; SDS, standard deviation score; OR, odds ratio ; Gy, Gray ; ALL, acute lymphoblastic leukaemia; BMI, body mass index ; HR, high risk ; y, years ; vs., versus.

of a malignant lymphoma. However, the number of included CRT-treated survivors in this study was very small (n = 6). A limitation of all these DEXA-studies is the small size of the cohorts (ranging between 23 and 95 survivors).

Warner et al[38] measured skinfold thickness in 35 CRT-treated ALL-survivors in addition to measurement of BMI and %fat mass at DEXA. Skinfold thickness as well as whole body %fat was increased in females. Jarfelt et al[44] measured waist- and hip-circumferences in ALL-survivors. Besides an increased BMI and an increased %fat mass at DEXA, they also found significantly a higher waist circumference ($P = .003$) and a higher waist-to-hip ratio ($P = .005$) in CRT-treated men compared with men treated without CRT (n = 7).

In conclusion, cross-sectional analysis of body composition showed that patients treated with CRT had higher %fat at DEXA compared to patients treated with chemotherapy only, while not all studies showed different BMI in CRT-treated compared with non-CRT-treated survivors. Especially female survivors treated with CRT are at increased risk for obesity in later life. Until now, most studies investigating change of body composition were performed in ALL-survivors.

4.4. Effect of chemotherapy on body composition in childhood cancer survivors

Meacham et al[24] studied the prevalence of underweight or obesity in relation to chemotherapy. They showed that risk for being underweight was increased in female survivors treated with alkylating agents (odds ratio 1.8; $P = .01$) and in female and male survivors treated with a combination of alkylating agents and anthracyclines (odds ratios, respectively, 1.4 ($P = .03$) and 2.1 ($P = .005$)). The risk of obesity was only increased in survivors treated with CRT, but not in survivors treated with chemotherapy only. Unfortunately, they did not differentiate between survivors treated with or without corticosteroids and they did not adjust for follow-up duration and selection bias. On the other hand, other authors studied the effect of corticosteroids on change in body composition, but did not differentiate between cytostatic drugs.

Most studies investigating change in body composition after corticosteroid treatment were cross-sectional and were performed in (small) cohorts of ALL-survivors. Van der Sluis et al[49] studied BMI in 23 ALL-survivors, who were treated with chemotherapy only (including corticosteroids). After mean 9.6 (7.9–11.4) years post-treatment, no significant differences in BMI were found. Also Sklar et al[45] found no effect of glucocorticosteroids on body composition measured by BMI in 126 ALL-survivors treated with corticosteroids (88 also had CRT). Nysom et al[48] studied BMI in survivors of a malignant lymphoma (23 Hodgkin survivors and 21 non-Hodgkin survivors) of which 37 also received corticosteroids. After

median follow-up of 8.7 (1.4–24.5) years post-treatment BMI values were not significantly different in survivors compared with controls. On the other hand, others observed that at cessation of treatment most obese children belonged to those who received 35 weeks dexamethasone during a period of 2.25 years (43% was obese; $P < .05$). The effect of dexamethasone on increasing BMI seemed to be temporary, while 4 years post-treatment most obese children were found in those treated with combination of prednisolone and dexamethasone (without CRT). In this group, 44% was classified as obese ($P < .05$). Follow-up in this study was no longer than 4 years post-treatment[10]. Finally, Reilly et al[50] studied the effect of glucocorticoid therapy on body composition in ALL-survivors during treatment. At respectively, 1 and 2 years post-diagnosis, mean increase in BMI was significantly higher compared to reference data ($P < .05$). No differences were found between dexamethasone-treated and prednisone-treated survivors.

As far as we know, only one study in survivors of childhood brain tumour studied the effect of corticosteroids on body composition (measured by BMI)[12]. In that study no relation was observed between change in body composition and treatment with glucocorticosteroids. The brain tumour survivors received corticosteroids on a continuous base for a maximum of 6 months, while ALL-patients usually receive corticosteroids intermittently during a much longer period. For this reason, comparison of body composition between corticosteroid-treated brain tumour survivors and corticosteroid-treated ALL-survivors is troublesome.

Measurement of body composition by DEXA was performed in ALL-survivors in several studies[43,44,47,49]. Van der Sluis et al[49] found no abnormal body composition at DEXA after mean follow-up of 9.6 years post-treatment, despite high-dose dexamethasone during therapy. Also, Nysom et al[47] and Jarfelt et al[44] found no increase in %fat mass at, respectively, median 7.6 years and 20 years after corticosteroid treatment. In contrast, van Beek et al[43] showed that %fat was increased in prednisolone-treated survivors ($P < .05$) 12.7 years post-diagnosis, whereas %fat was normal in the dexamethasone-treated group. Also, Nysom et al[48] performed DEXA in 44 survivors of a malignant lymphoma and found an increased mean whole-body %fat in survivors ($P = .0001$) after median 8.7 years post-treatment. They found no relationship of whole-body %fat *z*-score with cumulative dose of corticosteroids, sex, age at diagnosis or age at follow-up.

In conclusion, in childhood ALL-survivors an increased fat mass was found during the first years after corticosteroid treatment. It is still not clear if the change in body composition is temporary or persistent. Furthermore, cytostatic drugs may cause underweight. However, these results were based on only one study and no information was given about the timing of this weight change. Longitudinal prospective research is needed to get insight

in the long-term effect of corticosteroids and cytostatics on body composition.

4.5. Timing in change of body composition after childhood cancer treatment

Timing of appearance of obesity in ALL-survivors is not quite clear. It has been suggested that dexamethasone-treatment causes a temporarily increase in BMI during and shortly after treatment[10]. Didi et al[42] suggested that boys showed a more gradual increase in BMI from diagnosis to attainment of final height ($P = .001$), while girls showed an increase in BMI especially during treatment ($P = .02$), and no significant increase in BMI between cessation of therapy and attainment of final height. To date, most studies were performed cross-sectionally. In order to describe timing of change in body composition, longitudinal studies are necessary. A recent longitudinal prospective study in 618 ALL-survivors showed that BMI *z*-scores started to increase shortly after diagnosis, first as a result of decrease in height *z*-scores and subsequently as a consequence of increase in weight *z*-scores. No differences were found between CRT-treated and non-CRT-treated survivors. BMI *z*-scores increased in all ALL-survivors with age at diagnosis below 13 years[40]. Furthermore, Marinovic et al[51] performed longitudinal evaluation of body composition in corticosteroid-treated ALL-survivors. BMI and DEXA were assessed at median 2.2 (0.1–3.1) years post-treatment. They found no increase of mean BMI compared to healthy controls ($P = .08$), while median %body fat was higher in patients ($P = .05$). At a subsequent evaluation 1 year later, no differences in body composition were found between patients and controls ($P = .94$). These results suggest a temporary increase in body mass parameters after corticosteroid treatment[51]. Also Sklar et al[45] studied BMI at several time points (at diagnosis, at end of treatment and at attainment of final height) and found that patients treated with CRT had a significantly increased BMI-SDS between diagnosis and end of treatment ($P < .001$), while in patients treated with only chemotherapy BMI-SDS remained unchanged. CRT was an independent predictor of being overweight at attainment of final height. A prospective study on body composition during 2 years ALL-treatment in 14 patients with either dexamethasone or prednisolone and either 6-mercaptopurine or 6-thioguanine[39] revealed that BMI standard deviation scores (values calculated from the 1990 British reference data) were greater at 1 and 2 years post-diagnosis than at diagnosis. Furthermore, after 2 years of treatment, BMI was higher than expected for the normal population. Results of DEXA showed that at 6, 12 and 24 months of treatment %fat mass was higher than at diagnosis, suggesting that obesity develops during treatment[39]. In conclusion, there is need for additional longitudinal prospective studies during and after cancer treatment, with or without CRT and/or chemotherapy, in order to gain more insight into the timing of development of obesity.

5. UNDERLYING MECHANISMS OF CHANGE IN BODY COMPOSITION IN CHILDHOOD CANCER SURVIVORS

Overweight cq. obesity as well as underweight has been shown to have negative consequences for general health. Increased cardiovascular risk has been described in patients with increased body fat[4,19], while on the other hand, underweight also affects general health. To prevent the development of abnormal change in body composition, we need to understand the underlying mechanisms. Hypotheses about potential underlying mechanisms are discussed below.

5.1. Disturbed energy balance during and after childhood cancer treatment

Some studies showed a relationship between positive energy balance during ALL-therapy and development of increased BMI during and after treatment. Reilly et al[50] found that energy intake was increased in periods of steroid treatment compared with periods without steroid treatment. This increase in energy intake seemed to be temporary. Others showed normal energy intake in childhood cancer survivors compared with healthy controls, but a reduced physical activity/energy expenditure. This could be a factor of importance in the development of obesity[15,16].

Reduced energy expenditure may play a role in the development of an increased BMI in general population, as well as in cancer survivors during and after cancer treatment. Marinovic et al[51] studied physical activity in 37 ALL-survivors (all treated with prednisone, but without CRT) at median 2.2 and 3.2 years post-treatment. At the first evaluation, survivors were less physical active ($P = .02$) and had a higher median %body fat ($P = .05$) compared to controls, while mean BMI was only slightly higher ($P = .08$). At baseline, no relation was found between body composition (lean body mass and %body fat mass) and physical activity. One year later, physical activity and %body fat were similar in ALL-survivors and matched controls. Another study[52], in 35 ALL-survivors (all treated with prophylactic CRT and chemotherapy) and 21 survivors of other malignancies (treatment with chemotherapy only, no CRT; at least 1.5 years post-treatment), showed that children treated for ALL had reduced energy expenditure at all the submaximal exercise levels (tested by cardiopulmonary fitness) compared with survivors of other malignancies and with controls. Peak oxygen consumption after controlling for free fat mass in male and female ALL-survivors was, respectively, 53.1 and 46.4 ml/kg/min (in controls, respectively, 61.5 and 57.3 ml/kg/min; $P < .05$). Furthermore, energy expenditure was significantly negatively correlated with body fat (measured by DEXA) after controlling for body weight. Based on the small number of patients, it remains unclear if obesity develops as a result of reduced energy expenditure and how long after treatment this persists or if weight gain develops as a result of excess intake. However, others[12,52] showed that after treatment with

CRT or cranial surgery, hypothalamic damage may cause changes in energy metabolism. This may cause a disturbed energy balance (disturbed energy intake and/or energy expenditure), which might be related to the development of hypothalamic obesity. In Section 5.2, hypothalamic damage in relation to the development of obesity will be discussed further.

Another factor in development of (adult) obesity may be age of adiposity rebound (AR). AR refers to the increase in BMI that occurs after a nadir observed in children around the age of 5.5 years. It has been shown that children displaying an early AR, before the age of 5.5 years, are at risk for adult obesity[53]. A study performed in 39 girls from the general population showed that those who had an AR below 5 years of age had a faster rate of fat gain compared with girls who have AR at a later age[54]. Differences in BMI during AR were caused specifically by alterations in body fat and not by alterations in lean mass or height. As far as we know, only one study in childhood cancer survivors was performed in order to describe age of AR[55]. In that study timing of AR was studied in ALL-survivors, treated before the age of 30 months. Respectively, 42.6% and 80.9% of the survivors showed AR at the age of 3 and 4 years, while, respectively, 4.5% and 21.2% in controls ($P < .001$). A study in childhood brain tumour survivors (n = 148; 89/148 received CRT) showed that survivors treated before the age of 7 years had a greater increase in BMI compared with those diagnosed after the age of 6 years[12]. In conclusion, survivors with early AR or survivors treated before assumed AR, showed higher increase in BMI post-treatment compared with those with late AR (above age 5–6 years) or with those treated at age over 6 years. An early AR may be one of the explanations for the reported higher prevalence of obesity in children treated before the age of 4 years[41]. Until now, little is known about the underlying cause of an early AR in childhood survivors—is it induced by the specific cancer treatment (i.e. corticosteroids or radiotherapy) or related to the type of cancer or probably to a specific genetic predisposition? For answering these questions, additional (prospective) studies should be performed in children treated for cancer with cytostatics and/or radiotherapy and treated before the expected age of AR. If early AR is confirmed to be a risk factor for development of obesity, patients treated before the age of 5 years might be counselled to prevent undesired weight gain after cancer treatment.

5.2. Hypothalamic damage after earlier childhood cancer (treatment)

Cranial surgery and/or CRT may cause damage to the hypothalamic–pituitary axis. Studies in childhood brain tumour survivors showed that the risk of obesity was especially increased if the hypothalamic region was involved either in the tumour site or in the irradiation field. In a longitudinal retrospective BMI-analysis (from birth till median 6.2 (range: 0.1–21.5) years post-diagnosis) in 90 childhood craniopharyngioma patients, survivors

with hypothalamic involvement of the craniopharyngioma (n = 48) had higher standard deviations of BMI at time of diagnosis and at annual follow-up intervals[13]. At latest follow-up, BMI standard deviation was 5.1 in survivors with hypothalamic involvement versus 0.4 in those without hypothalamic involvement ($P < .001$). Only 10% of survivors with hypothalamic involvement preserved normal weight (versus 69% of survivors without hypothalamic involvement), independent of CRT-treatment.

Damage to the hypothalamic–pituitary axis may result in growth hormone deficiency (GHD). Gurney et al[21] studied prevalence of GHD in 75 ALL-survivors treated with (n = 50) or without (n = 25) CRT (mean 24.6 ± 4.8 years post-diagnosis) and found that 58% of CRT-treated survivors had GHD. Remarkably, even non-CRT-treated ALL-survivors have an (increased) risk of GHD: 5 out of 24 (21%) ALL-survivors without CRT-treatment had GHD. Also, Birkebaek et al[56] found GHD in 2 out of 11 ALL-survivors treated with chemotherapy only. In both studies no explanation is given for GHD occurring in non-irradiated survivors. Whether this is a valid observation needs to be studied in larger cohorts. As current studies use different criteria and tests for assessment of GHD, the results are difficult to compare. Gurney's study showed that BMI and waist-to-hip ratio were higher among those with lower than normal peak growth hormone (GH) levels[21]. In a small study on craniopharyngioma survivors (n = 15) with established GHD, %abdominal fat was higher compared with healthy BMI-matched controls without GHD[14]. In conclusion, GHD may be an important factor in development of obesity in these survivors.

GH status and cardiovascular risk factors were assessed in three Swedish studies in CRT-treated childhood ALL-survivors with GHD[17,32,33]. GH replacement therapy was started in the survivors with confirmed GHD and follow-up of cardiovascular risk factors during this treatment was performed[32,33]. Firstly, Link et al[17] studied cardiovascular risk factors cross-sectionally at median 16.7 (6.3–23.9) years post-treatment in ALL-survivors without GH replacement therapy. They found that cardiovascular risk factors, such as fat mass, were increased in survivors compared with healthy controls. In a prospective study in 11 adult ALL-survivors with a severe radiation induced GHD, who received GH replacement therapy from median 20.5 (13.5–22.5) years post-treatment, BMI and %fat mass (measured by BIA) were determined at baseline (just before start of treatment) and after 12 months treatment[32]. At baseline, survivors had higher %fat mass compared with BMI-matched controls ($P = .05$), while after 12 months a decrease in %fat mass was seen compared with baseline measurements ($P = .03$). However, no change in BMI was found. Most recently, Follin et al [33] evaluated the effect of 24-months GH replacement therapy on cardiovascular risk factors and cardiac function in 18 ALL-survivors with confirmed GHD. After 24 months of GH therapy (n = 13), no change in BMI was found compared

with baseline measurements. Until 12 months of treatment, the %fat mass decreased ($P = .002$), whereas after 24 months no differences in %fat mass were seen. At baseline, 6 survivors and 1 control subject fulfilled the definition of the metabolic syndrome, while after 12 months of GH replacement therapy, only one survivor and after 24 months none had the metabolic syndrome. Systolic heart function, measured as fractional shortening, was within normal ranges before GH replacement therapy (median (range) 36 (22–46)%) and increased after 24 months of treatment (40 (29–48)%; $P = .03$). Others also studied the effect of GH replacement therapy in childhood brain tumour- and ALL-survivors (n = 27) and found after 12–18 months of GH treatment no change in either BMI or %fat mass[57].

In conclusion, GHD increases the prevalence of cardiovascular risk factors and in childhood cancer survivors CRT and GHD are strongly related. However, not all survivors with GHD had CRT. GH replacement therapy decreases %fat mass, while BMI remains unchanged. According to Follin et al., treatment with GH decreases the prevalence of metabolic syndrome in survivors with GHD and probably decreases cardiovascular risk[33]. Additional long-lasting prospective studies, in more extensive cohorts of survivors with GHD, will be necessary to describe the effect of GH replacement therapy on cardiovascular risk factors, and to clarify whether this will lead to improved cardiovascular outcome. Based on present studies GHD plays a role in development of obesity after treatment for childhood malignancies.

5.3. Gonadal dysfunction after earlier childhood cancer treatment

Until now, little is known about a possible relationship between gonadal dysfunction and development of obesity and other cardiovascular risk factors in childhood cancer survivors. As far as we know, Neville et al[37] were the only ones that studied this association in childhood cancer survivors. At median 12.9 (range: 2.3–33.6) years post-diagnosis, they examined prospectively the prevalence of overweight/obesity, abdominal obesity and hyperinsulinaemia, impaired glucose intolerance or diabetes mellitus in 248 childhood cancer survivors (n = 36 pre-pubertal; n = 88 pubertal; n = 124 adult). They compared the results of the survivors with those of healthy controls and found that untreated hypogonadism was an independent risk factor for the development of hyperinsulinaemia, impaired glucose intolerance or diabetes mellitus. Other studies about a possible relationship between hypogonadism and cardiovascular risk factors were performed in survivors of adult cancer. One study showed a relationship between ovarian dysfunction and increased serum lipid levels[58] and another one showed that survivors of testicular cancer with a hypogonadism had a higher waist-to-hip ratio ($P = .045$) and higher diastolic blood pressure ($P = .014$) than survivors without hypogonadism[59]. Because development of gonadal dysfunction after childhood cancer treatment has been widely described[60-64], we

need to elucidate the possible relationship between gonadal dysfunction and abnormal changes in body composition, also in childhood cancer survivors.

5.4. Leptin resistance and genetic factors in development of abnormal body composition

Leptin is a peptic hormone which is mainly synthesised by white adipose tissue and secreted into the peripheral blood[65-67]. It circulates in plasma in a free form or bound to it's receptor (LEPR) in the hypothalamus[67]. Normally, an increase in leptin level causes a decreased appetite and food intake and increased energy expenditure and it plays a role in the regulation of metabolism and body weight[68]. With increasing fat mass, leptin level increases exponentially, thus reflecting the amount of stored fat[67]. A prospective study in men with hypercholesterolaemia showed that leptin is an independent predictor of risk of a future coronary event, also after adjustment for BMI and other classic factors[69]. Above a threshold of 25–30 ng/ml serum leptin levels are not translated into proportional increases in cerebrospinal or brain leptin levels. This, in turn, may result in leptin resistance and obesity. Most obese humans have increased leptin levels, indicating that in most of them obesity is a leptin-resistant state[68].

In obesity studies in childhood cancer survivors, serum leptin concentrations are increasingly measured in order to establish the possible role of leptin as a biochemical parameter in assessment of body composition. Most authors combined measurement of serum leptin with other methods for measurement of body composition, such as BMI, DEXA and BIA. Wallace et al[70] performed a longitudinal prospective study of circulating leptin levels and BMI in 19 childhood ALL-patients during the first 16 weeks of treatment. Blood samples were taken every 1–2 weeks. Patients were randomised for either prednisolone (n = 12) or dexamethasone (n = 7) as a component of induction therapy. A narrow correlation was found between serum leptin concentrations and BMI, and after 4 weeks of high dose steroids the leptin/BMI ratio was increased. Probably a disruption of the normal relationship between leptin and BMI exists. The authors suggest that it might be due to an increase in fat mass. Furthermore, they showed that dexamethasone was much more potent than prednisolone at increasing leptin levels. Davies et al[39] studied serum leptin concentration during entire treatment of ALL (follow-up 2 years; n = 14) and found, besides excess adiposity measured by BMI and DEXA, that serum leptin concentrations were increased during 24 months of ALL-treatment ($P < .05$).

Several authors studied serum leptin concentrations after completion of treatment for childhood cancer[17,33,46]. Most of these studies were performed in survivors treated with CRT. At median (range) 17.8 (6.8–28.6) years post-CRT-treatment Brennan et al[46] found

that leptin concentrations were higher in CRT-treated ALL-survivors (n = 32) compared with healthy controls ($P < .01$), especially in survivors with a severe GHD (without GH replacement therapy). No relation with gender was shown. Hyperleptinaemia may be a consequence of radiation-induced hypothalamic damage. Furthermore, GH deficiency, as result of hypothalamic damage, may aggravate hyperleptinaemia. Also Link et al[17] found higher leptin levels in CRT-treated ALL-survivors (median 16.7 (range 6.3–23.9) years post-treatment). After adjustment for gender, serum leptin and leptin/kg fat mass were higher among the female patients compared with female controls ($P = .001$). Others studied leptin concentration in GH deficient ALL-survivors before and after GH replacement therapy[33]. After 12 months of GH treatment serum leptin and leptin per kilogram fat mass was significantly lower compared with baseline measurements. After 24 months of GH treatment only a decline in serum leptin was seen. The decrease in serum leptin after 24 months of GH treatment may be a result of the decrease in fat mass (measured by BIA and DEXA) induced by GH treatment. Finally, Birkebaek et al[56] evaluated endocrinological status 10–21 years post-treatment in 30 childhood ALL-survivors. Eighteen of them received a combination of chemotherapy and CRT, whereas 12 received chemotherapy only (including prednisolone). Serum leptin was higher in the CRT-treated group as compared with the non-irradiated group (median 23.0 ng/ml versus 7.0 ng/ml, $P < .02$). Serum levels were not dependent on GH status.

As far as we know, the only genetic study about obesity susceptibility in childhood cancer survivors was performed by Ross et al[71]. They showed that a genetic variation in the leptin receptor (LEPR Gln Arg polymorphism) might stimulate susceptibility to obesity in childhood ALL-survivors. A higher frequency of the Arg/Arg genotype was found in females who had a BMI ≥ 25 kg/m^2. Furthermore, Arg homozygous females who were treated with more than 20 Gy CRT had a 6-fold increased chance of having a BMI ≥ 25 kg/m^2 compared with females with only one or no Arg allele ($P = .002$). No differences were observed in male survivors. Female ALL-survivors who are homozygous for the Arg genotype have lower leptin binding affinity, so this seems a functional single nucleotide polymorphism (SNP). Possibly, the Arg genotype in the presence of CRT may further decrease LEPR binding affinity. More research is needed to confirm the value of above-mentioned polymorphism and to find new candidate genes. A genetic study in general population (as part of the Framingham Heart Study) studied DNA samples in five different cohorts[72]. A strong association between the SNP rs7566605 and obesity (measured as BMI) was found in four of the five cohorts. rs7566605 is part of the INSIG2 gene. INSIG2 is a candidate gene which probably affects BMI, because the protein product inhibits the synthesis of fatty acid and cholesterol. This candidate gene may also play a role in development of obesity in childhood cancer survivors, but needs further exploration.

In conclusion, during corticosteroid treatment serum leptin increases, but little is known about leptin-status after corticosteroid treatment. On the other hand, survivors post-CRT-treatment showed increased serum leptin levels up to 18 years post-treatment, which is associated with overweight. Thus far, results about the effect of GHD on serum leptin level are conflicting. Leptin levels may turn out to be a method for measuring the amount of body fat. Furthermore, polymorphisms in the obesity gene(s) may predict susceptibility to obesity before starting cancer treatment. Information about susceptibility of development of obesity may be useful for intervention strategies, i.e. prevent actively (for example by early consultation of a dietician). As the results up to now are based on small cohorts of patients and less is known about timing of leptin increase, prospective longitudinal evaluation of serum leptin levels during and after cancer treatment with CRT, corticosteroids and/or chemotherapy is warranted.

6. DISCUSSION

Several interesting data about body composition in childhood cancer survivors emerged from recent literature. We reviewed studies on the prevalence of abnormal body composition after earlier childhood cancer treatment and described relations between abnormal body composition and specific cancer treatment. Most data concern increased prevalence of obesity in female ALL- and brain tumour-survivors treated with CRT. These data are not only based on BMI, but also on increased fat mass found at DEXA. In order to prevent obesity in these survivors, intervention strategies need to be explored. Knowledge of the underlying mechanisms is essential in development of intervention strategies. In this review we addressed the underlying mechanisms in obesity and found that several factors may play a role. Firstly, CRT-treatment and/or location of tumour may cause hypothalamic damage, which is related to an increased risk of obesity, in particular if GHD is present. Secondly, decreased physical activity during cancer treatment, which may continue post-treatment, may play a role in development of obesity. However, no information is available about the underlying mechanism of decreased physical activity in childhood cancer survivors, i.e. timing and genetic influences. Furthermore, influence of increased energy intake needs further exploration. In addition, patients who are treated before suspected AR or patients who have an early AR (before the age of 5 years; probably induced by cancer (treatment)) have an increased risk of being obese at a later age. Other possible underlying mechanisms in development of obesity may be gonadal dysfunction or genetic susceptibility to obesity. Data on the possible relationship between gonadal dysfunction and obesity and/or other cardiovascular risk factors in childhood cancer survivors are scarce. Recently, Neville et al[37] found that untreated hypogonadism in survivors is an independent risk factor for the development of hyperinsulinaemia, impaired glucose intolerance or diabetes mellitus. In conclusion, obesity appears to be

a problem in childhood cancer survivors treated with CRT. Further exploration is needed, because increased weight is one of the components of the metabolic syndrome, which is in turn a risk factor for developing cardiovascular disease[18]. In order to prevent obesity, we need to unravel the multiple mechanisms that may play a role in its development. Thus far, hormonal axes may form important targets for intervention with the aim to reduce cardiovascular risk. Prospective evaluation of several parameters needs to be started at diagnosis of childhood cancer, to be continued at several time points during and after treatment. For example, assessment of physical activity, GH testing and determine gene polymorphisms which are related to an increased risk in developing obesity.

Results of the CCSS showed that childhood cancer survivors, treated with cytostatic drug, have an increased risk of being underweight[24]. The risk of underweight after treatment with cytostatic drugs is thus far only described by the CCSS and only studied by BMI. Little is known about the underlying mechanism of underweight in cancer survivors. Hypothetical, BMI in survivors treated with cytostatic drugs decreases during treatment and continues to stay at a lower level post-treatment. However, there are no data to support this. Moreover, before unravelling the underlying mechanism(s) of development of underweight in childhood cancer survivors, the increased prevalence of underweight in these survivors described by CCSS has to be established in additional studies. Furthermore, the use of BMI for measurement of body composition is not indisputable proven: some studies showed a normal BMI, while fat mass was increased at DEXA. Studies that use a combination of BMI and DEXA to establish a possible relationship between a decreased BMI and a decreased fat mass are warranted for the appraisal of underweight and to assess if underweight really is a problem in childhood cancer survivors. If underweight is an established problem, additional research is needed to gain insight in the underlying mechanisms.

We also tried to elaborate the presumed relationship between corticosteroid treatment and the development of obesity. The available data on the effect of corticosteroids on body composition are conflicting. Corticosteroids apparently cause a temporarily increase in BMI, but little is known about the long-term effect of corticosteroid treatment on body composition.

Finally, we described new methods for analysis of body composition. Serum leptin measurements and BOD POD may be promising techniques for evaluation of body composition in childhood cancer survivors. Additional studies are warranted to establish the predictive value of these new methods compared with current measurements (i.e. BMI, DEXA, BIA). Another promising area of research is created by assessment of gene

polymorphisms and new candidate genes that play a role in the development of obesity.

7. CONCLUSION

Most studies on body composition in childhood cancer survivors are small and retrospective. Survivors of ALL and brain tumours who have been treated with CRT are at risk for weight gain, whereas survivors of other childhood cancers seem to be at risk for underweight. The impact of obesity as well as underweight on survival and morbidity is not really known. In the general population, prevention of obesity is important in order to prevent cardiovascular disease. Therefore, prevention of obesity and treatment of overweight may be even more important in childhood cancer survivors who often have a history of potential cardiotoxic cancer treatment and therefore are prone to develop cardiovascular disease. Extensive longitudinal prospective studies on body composition in childhood cancer patients from the start of treatment are warranted. Measuring body composition (by several methods, i.e. BMI, DEXA and BOD POD), taking blood samples (genetic polymorphisms, lipid profile, GH testing, gonadotrophins) and quantitative measurement of physical activity during follow-up seems to be justified in standardized research follow-up programs to investigate their relevance for childhood cancer survivors. This enables the search for underlying mechanism(s), which play a role in change of body composition in childhood cancer survivors and may serve as intervention targets.

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CHAPTER 3

Changes in Body Mass Index after Childhood Cancer Treatment: a Longitudinal Evaluation

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ABSTRACT

Background. An abnormal body composition has been described as cardiovascular risk factor. In childhood cancer survivors with potentially cardiovascular-toxic treatment, we evaluated the prevalence of under- and overweight after reaching final height, the change in body mass index (BMI) post-treatment until reaching final height and its association with cancer treatment.

Methods. We included 377 survivors treated between 1976-1999 for childhood cancer with anthracyclines, platin and/or radiotherapy. From the medical records, height and weight at diagnosis and at ≥3 time points (≥5 years post-treatment) were collected to calculate BMI. Underweight was defined as a BMI <18·5 kg/m^2, and overweight as a BMI ≥25·0 kg/m^2. Prevalence of under- and overweight after reaching final height was compared with that of a population-based birth cohort from the Netherlands.

Findings. After reaching final height, prevalence of underweight was higher in the survivors (14% vs. 4%), while prevalence of overweight was comparable to the reference population (19% vs. 22%). Survivors who received cranial-/craniospinal-irradiation (CRT) had a higher BMI at completion of treatment (+0·59 kg/m^2; p=0·020) and were more overweight after reaching final height (OR 2·23; 95% CI 1·17-4·26). Survivors who received a higher anthracycline dose had a lower rate of annual BMI increase post-treatment (-0·03 kg/m^2/year/100 mg/m^2; p=0·046) and were more underweight after reaching final height (by 100 mg/m^2 anthracyclines; OR 1·27; 95% CI 1·04-1·56).

Interpretation. CRT-treated childhood cancer survivors had an increased BMI at completion of treatment and after reaching final height. Survivors treated with a higher anthracycline dose can develop underweight during follow-up post-treatment.

INTRODUCTION

Cardiovascular late effects in childhood cancer survivors have been widely described.[1-4] One of the known risk factors for cardiovascular disease is an abnormal body composition, which is frequently characterized by body mass index (BMI). Calle and co-workers[5] described the association between BMI and the risk of death in a cohort of more than one million US adults. They found a J-shaped curve for risk of all-cause death (including cardiovascular death); a high BMI (≥25 kg/m^2) was the most predictive of death, but the risk also increased in persons with a low BMI (<20·5 kg/m^2).[5]

Overweight is observed as a late effect after childhood cancer treatment, especially in cranial irradiated survivors of acute lymphoblastic leukaemia and brain tumours.[6,7] Underweight is a less well-known late effect in childhood cancer survivors. Meacham and co-workers[8] performed a cross-sectional BMI analysis and reported more underweight in childhood cancer survivors compared with a national reference population and sibling controls. To gain insight into the timing of the development of abnormal body composition, longitudinal evaluation is warranted. So far, only a limited number of studies have evaluated BMI at several time points during and/or after childhood cancer treatment.[7,9-12] A longitudinal evaluation of BMI from diagnosis until adult height in survivors of a haematological malignancy has shown overweight at diagnosis as the most significant and strongest predictor of overweight/obesity at adult height.[9] Thus far, no studies on BMI change were performed in survivors of a solid tumour, neither in association with development of underweight.

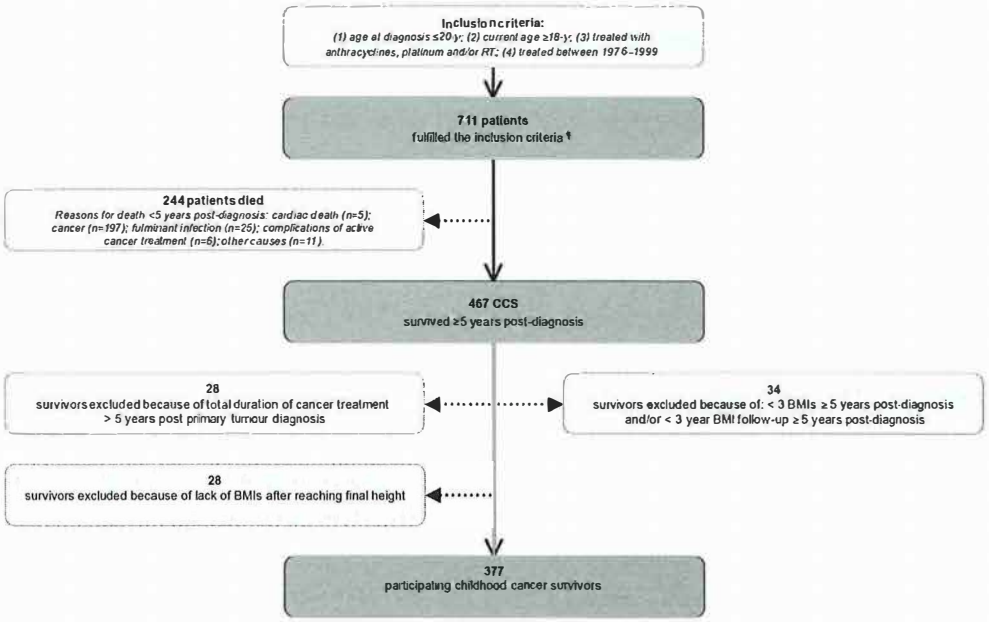
We performed a longitudinal evaluation of BMI in a cohort of childhood cancer survivors with the objectives: (1) to assess the prevalence of under- and overweight after reaching final height; (2) to assess the association between under- and overweight after reaching final height and previous cancer treatment; and (3) to assess the BMI change from end of cancer treatment until reaching final height and its association with cancer treatment.

METHODS

Study participants (Figure 1)

Participants were included as part of a study on cardiovascular disease and cardiovascular risk factors in childhood cancer survivors with the following eligibility criteria: (a) diagnosis between 1976-1999; (b) potentially cardiovascular-toxic cancer treatment at the University Medical Center Groningen (anthracyclines, platinum and/or radiotherapy (RT) of head, neck, spine or trunk); (c) age at diagnosis ≤20 years; (d) current age ≥18 years; and (e) no pre-existent cardiovascular disease and/or Down syndrome. Eligibility criteria were fulfilled by 711 patients of whom 244 died within 5 years post-diagnosis. In total, 467

Figure 1 Flow diagram of the included and excluded childhood cancer survivors.



Note. CCS, childhood cancer survivors; RT, radiotherapy; exclusion criteria: patients with Down syndrome (n = 7) or existent cardiac failure (n = 0).

patients survived ≥5 years post-diagnosis. Additional eligibility criteria for the BMI analysis were: (a) childhood cancer treatment completed within 5 years post-diagnosis; (b) three or more consecutive BMI measurements ≥5 years post-treatment and covering a follow-up period of ≥3 years; and (c) a known BMI after reaching final height. In total, 377/467 (81%) survivors fulfilled the eligibility criteria. Those with a late relapse or a secondary tumour were censored until one year before the late relapse or secondary tumour.

Methods

Height and weight at diagnosis, on completion of treatment and at several time points post-treatment were collected from the medical records. BMI was calculated by the formula: weight (kg)/(height)^2(m^2). For adults (age ≥18 years), underweight was defined as a BMI <18·5 kg/m^2, overweight as a BMI ≥25 kg/m^2 and obesity as a BMI ≥30 kg/m^2. In children (age <18 years), BMI reference values of underweight, overweight and obesity as published by Cole and co-workers[13] and Van Buuren and co-workers[14] were used. Final height was defined as the standing height reached when height increased less than 1·5 cm in two consecutive years of measurement. If survivors had more than one known BMI after reaching final height, we used the first one that was measured after 5 years post-treatment.

The prevalence of underweight, overweight and obesity after reaching final height in the survivors was compared with the prevalence of underweight, overweight and obesity in a population-based birth cohort (born between 1975 and 1978) from the background population of the same geographical region as the survivors, namely the northern part of the Netherlands (n=590; median (range) age 21·3 (19·7-23·4) years).[15,16] Weights and heights were collected between 1998 and 1999. The median year of the retrospective BMI assessment in the current study was 1999.

Definition of cancer treatment groups

The chemotherapy subgroups were defined as (1) combination chemotherapy including anthracyclines (doxorubicin, daunorubicin), (2) combination chemotherapy including platinum (cisplatin, carboplatin) and (3) any chemotherapy with no RT. The RT subgroups were defined as (1) cranial-/craniospinal RT (CRT), (2) chest-/neck RT, including mantle field, mediastinum, total lung, neck and/or spine, (3) abdominal RT, including abdomen, pelvic and/or spine and (4) total body irradiation (TBI). Given the era the cancer was diagnosed in our cohort (1976-1999), individual dosimetry on cranial structures was not available. Therefore, CRT dose was subdivided into <30 Gy and ≥30 Gy.

Data analysis and statistics

Statistical analyses were performed in SPSS Inc. version 14. For descriptive analyses, non-parametric tests (Mann-Whitney and Wilcoxon's tests) and median (minimum-maximum) were used, since the parameters have a non-Gaussian distribution. The prevalence of underweight, overweight and obesity after reaching final height was assessed and compared with the reference population. As the number of survivors with obesity was small in this study, we used underweight and overweight as primary outcome measurements. Univariate analysis was performed to compare treatment-related characteristics between the survivors with underweight after reaching final height and the survivors with overweight after reaching final height. Multiple logistic regression analysis was used to assess the association between the dependent variables underweight, normal weight and overweight after reaching final height, and the several cancer treatment modalities. In the regression analysis, we adjusted for age at diagnosis, sex, total duration of cancer treatment, age at BMI measurement after reaching final height and for under- and overweight at diagnosis. Since previous studies have shown different outcomes by sex [6,8], possible effect modification by gender was investigated by introducing an interaction variable between sex and the treatment modalities in the regression analysis. Finally, by multilevel analysis[17], BMI at completion of treatment and the annual BMI change afterwards until reaching final height was assessed in association with the previous cancer treatment. Two-sided p-values ≤0·05 were considered significant.

RESULTS

Prevalence of under- and overweight after reaching final height

The inclusion criteria were fulfilled by 377 survivors (209 male [55%]). The median (range) age at diagnosis was 9·3 (0·0-20·5) years. The median age of the first measured BMI after reaching final height at ≥5 years post-treatment was 20·0 (12·7-42·7) years. Additional characteristics are summarized in table 1. Compared with the reference population,[15,16] the prevalence of underweight was higher in the survivors (14% [53/377] vs. 4% [25/590]; p<0·001), whereas the prevalences of overweight (19% [73/377] vs. 22% [128/590]; p=0·384) and obesity were comparable (5% [17/377] vs. 5% [27/590]; p=0.961).

Treatment-related factors in survivors with underweight and survivors with overweight after reaching final height

The characteristics of the survivors with underweight (n=53), normal weight (n=251) and overweight (n=73) after reaching final height are summarized in table 2. The results of those with overweight were compared with those with underweight after reaching final height. Survivors with underweight after reaching final height had a significantly higher prevalence of underweight at diagnosis, 0-2 years post-treatment and 2-5 years post-treatment. Twenty-eight of the 107 (26%) survivors with underweight at diagnosis had underweight after reaching final height. Those with underweight after reaching final height received a higher cumulative anthracycline dose and were more often treated with TBI. Survivors with overweight after reaching final height had a higher prevalence of overweight at diagnosis, 0-2 years post-treatment and 2-5 years post-treatment. Fifteen of the 19 (79%) survivors with overweight at diagnosis had overweight after reaching final height. Those with overweight after reaching final height received more often CRT.

Association of under- and overweight after reaching final height and previous cancer treatment

The results of multiple logistic regression analysis are summarized in table 3. Underweight after reaching final height was associated with underweight at diagnosis (odds ratio (OR) 3·69; 95% confidence interval (CI) 1·91-7·09; p<0·001). In the adjusted model (including adjustment for underweight at diagnosis), underweight after reaching final height was associated with TBI and cumulative anthracycline dose, especially if anthracycline dose was >300 mg/m^2. Even after adjustment for previous CRT, underweight after reaching final height was associated with cumulative anthracycline dose >300 mg/m^2 and tended to be associated with TBI. (table 3)

Overweight after reaching final height was associated with overweight at diagnosis (OR

Table 1. Characteristics of the studied 377 childhood cancer survivors

Age at diagnosis – years *		9·3 (0·0 – 20·5)
Sex (male/female)		209/168
Age at BMI - measurement after reaching final height – years *		20·0 (12·7 – 42·7)
FU post-treatment after reaching final height – years *		8·4 (5·0 – 28·0)
Total duration of cancer treatment – years *		1·3 (0·1 – 4·9)
Prevalence of underweight at several time points (%)		
At diagnosis		107/344 (31·1%)
At 0-2 years post-treatment		90/370 (24·3%)
At 2-5 years post-treatment		53/367 (14·4%)
After reaching final height		53/377 (14·1%)
Prevalence of overweight at several time points (%)		
At diagnosis		19/344 (5·5%)
At 0-2 years post-treatment		33/370 (8·9%)
At 2-5 years post-treatment		48/367 (13·1%)
After reaching final height		73/377 (19·4%)
Diagnoses	**N**	**Percentage of 377 survivors**
Leukaemia	151	40
Brain tumour	47	12
Sarcoma	70	19
Malignant lymphoma	75	20
Blastoma	28	7
Germ cell tumour	6	2
Treatment modalities	**N**	**Percentage of 377 survivors**
Anthracyclines	264	70
Cumulative anthracycline dose >300 mg/m^2	67	18
Platin compounds	32	8
Any chemotherapy, no radiotherapy	133	35
Cranial-/craniospinal -irradiation	148	39
Dose of cranial-/craniospinal -irradiation		
1 – 29 Gy	82	22
≥30 Gy	66	18
Chest-/neck -irradiation [1]	90	24
Abdominal irradiation [2]	80	21
Total body irradiation	22	6

Note. *, median (range); [1], chest-/neck irradiation was defined as radiotherapy of mantle field, mediastinum, total lung, neck and/or spine; [2], abdominal irradiation was defined as radiotherapy of abdomen, pelvic and/or spine; BMI, body mass index; underweight, BMI <18·5 kg/m^2; normal weight, BMI 18·5-24·9 kg/m^2; overweight, BMI ≥25·0 kg/m^2; in children, BMI reference values of underweight and overweight as published by Cole and co-workers[13] and Van Buuren and co-workers[14] were used; final height, defined as the standing height reached when height increased less than 1·5 cm in two consecutive years of measurement; FU, follow-up; N, number.

Table 2. Characteristics of the survivors according to the 3 BMI categories after reaching final height

	Survivors with underweight after reaching final height (n=53)	**Survivors with normal weight after reaching final height** (n=251)	**Survivors with overweight after reaching final height** (n=73)	**p-value**
Age at diagnosis – years *	9·5 (0·0-19·5)	9·4 (0·4-20·5)	8·0 (1·1-20·1)	0·890
Sex (male/female)	31/22	140/111	38/35	0·474
Age at BMI measurement after reaching final height – years *	19·7 (15·6-28·4)	20·0 (12·8-41·7)	20·0 (12·8-41·7)	0·068
FU post-treatment after reaching final height – years *	8·5 (5·0-23·5)	7·9 (5·0-25·2)	10·5 (5·0-28·0)	0·102
Total duration of cancer treatment – years *	1·4 (0·2-4·9)	1·2 (0·1-4·2)	1·5 (0·1-4·6)	0·945
Prevalence of underweight at several time points, N⁰ (%)				
At diagnosis	28/48 (58)	69/229 (30)	10/67 (15)	**<0·001**
At 0-2 years post-treatment	32/53 (60)	55/246 (22)	3/71 (4)	**<0·001**
At 2-5 years post-treatment	31/53 (58)	22/243 (9)	0/71 (0)	**<0·001**
Prevalence of overweight at several time points, N⁰ (%)				
At diagnosis	1/48 (2)	3/229 (1)	15/67 (22)	**0·002**
At 0-2 years post-treatment	1/53 (2)	12/246 (5)	20/71 (28)	**<0·001**
At 2-5 years post-treatment	0/53 (0)	8/243 (3)	40/71 (56)	**<0·001**
Cumulative anthracycline dose (mg/m²) *	183 (0-640)	160 (0-600)	125 (0-600)	**0·036**
Diagnoses, N⁰ (%)				
Leukaemia	17/53 (32)	97/251 (39)	37/73 (51)	**0·037**
Brain tumour	4/53 (8)	30/251 (12)	13/73 (18)	0·096
Sarcoma	16/53 (30)	46/251 (18)	8/73 (11)	**0·007**
Malignant lymphoma	8/53 (15)	55/251 (22)	12/73 (16)	0·839
Blastoma	8/53 (15)	18/251 (7)	2/73 (3)	**0·017** [F]
Germ cell tumours	0/53 (0)	5/251 (2)	1/73 (1)	1·000 [F]
Treatment modalities, N⁰ (%)				
Anthracyclines	39/53 (74)	180/251 (72)	45/73 (62)	0·160
Cumulative anthracycline dose >300 mg/m²	18/53 (34)	38/251 (15)	11/73 (15)	**0·013**
Platin	6/53 (11)	21/251 (8)	5/73 (7)	0·525 [F]
Any chemotherapy, no radiotherapy	19/53 (36)	96/251 (38)	18/73 (25)	0·173
Cranial-/craniospinal irradiation	13/53 (25)	95/251 (38)	40/73 (55)	**0·001**
Dose of cranial-/craniospinal irradiation				
1 – 29 Gy	8/53 (15)	52/251 (21)	22/73 (30)	**0·050**
≥30 Gy	5/53 (9)	43/251 (17)	18/73 (25)	**0·029**
Chest-/neck irradiation [1]	13/53 (25)	58/251 (23)	19/73 (26)	0·849
Abdominal irradiation [2]	15/53 (28)	47/251 (19)	18/73 (25)	0·646
Total body irradiation	8/53 (15)	12/251 (5)	2/73 (3)	**0·017** [F]

Note: [Y], p-value of comparison between survivors with overweight after reaching final height versus survivors with underweight after reaching final height; *, median (range); [1], chest-/neck irradiation was defined as radiotherapy of mantle field, mediastinum, total lung, neck and/or spine; [2], abdominal irradiation was defined as radiotherapy of abdomen, pelvic and/or spine; [F], tested by Fisher's exact test; BMI, body mass index; underweight, BMI <18·5 kg/m²; normal weight, BMI 18·5-24·9 kg/m²; overweight, BMI ≥25·0 kg/m²; in children, BMI reference values of underweight and overweight as published by Cole and co-workers[13] and Van Buuren and co-workers[14] were used. Final height, defined as the standing height reached when height increased less than 1·5 cm in two consecutive years of measurement; FU, follow-up; N°, number.

Table 3. Multiple logistic regression analysis with underweight, normal weight and overweight after reaching final height as dependent variables

	Dependent variable = Underweight after reaching final height (n=377)		**Dependent variable =** Normal weight after reaching final height (n=377)		**Dependent variable =** Overweight after reaching final height (n=377)	
Independent variables [¶]:	OR[‖]	95% CI	OR[‖]	95% CI	OR[‖]	95% CI
Anthracyclines *(n=264)*	1·09	0·51 – 2·29	1·29	0·75 – 2·21	0·67	0·34 – 1·31
Cumulative dose of anthracyclines (by 100 mg/m^2)	**1·27**	**1·04 – 1·56**	0·90	0·77 – 1·06	0·94	0·77 – 1·16
Cumulative dose of anthracyclines >300 mg/m^2 *(n=67)*	**2·84**	**1·33 – 6·06**	0·58	0·31 – 1·11	0·84	0·37 – 1·94
Platin *(n=32)*	1·40	0·47 – 4·15	0·86	0·36 – 2·08	0·86	0·25 – 2·90
Any chemotherapy, no RT *(n=132)*	0·91	0·46 – 1·79	1·47	0·88 – 2·45	0·57	0·29 – 1·13
Cranial-/craniospinal RT *(n=148)*	**0·34**	**0·15 – 0·75**	1·05	0·63 – 1·77	**2·23**	**1·17 – 4·26**
Dose of cranial-/craniospinal RT subdivided in:						
0 Gy *(reference group) (n=229)*	1	--	1	--	1	--
1–29 Gy *(n=82)*	**0·32**	**0·12 – 0·85**	1·24	0·65 – 2·38	1·98	0·90 – 4·39
≥30 Gy *(n=66)*	0·37	0·12 – 1·13	0·87	0·44 – 1·73	**2·55**	**1·12 – 5·80**
Chest-/neck-RT [1] *(n=90)*	1·27	0·59 – 2·75	0·74	0·41 – 1·33	1·29	0·61 – 2·71
Abdominal-RT [2] *(n=80)*	1·80	0·87 – 3·75	0·72	0·40 – 1·30	0·91	0·41 – 1·99
Total body irradiation *(n=22)*	**3·28**	**1·11 – 9·68**	0·53	0·20 – 1·38	0·57	0·12 – 2·74
Combination of cranial-/craniospinal RT & total body irradiation & anthracycline dose >300 mg/m^2 in 1 model:						
Cranial-/craniospinal RT	0·45	0·19 – 1·04	0·86	0·49 – 1·49	**2·27**	**1·13 – 4·55**
Total body irradiation	2·88	0·92 – 8·97	0·50	0·19 – 1·33	0·78	0·16 – 3·82
Cumulative anthracycline dose >300 mg/m^2	**2·28**	**1·02 – 5·09**	0·54	0·28 – 1·03	1·16	0·48 – 2·81

Note: [1], chest-/neck-RT was defined as radiotherapy of mantle field, mediastinum, total lung, neck and/or spine; [2], abdominal RT was defined as radiotherapy of abdomen, pelvic and/or spine; [¶], multivariate regression analysis with "fixed" confounding variables age at diagnosis, sex, age at BMI measurement after reaching final height, duration of cancer treatment and under- and overweight at diagnosis; BMI, body mass index; underweight, BMI <18·5 kg/m^2; normal weight, BMI 18·5-24·9 kg/m^2; overweight, BMI ≥25·0 kg/m^2; in children, BMI reference values of underweight and overweight as published by Cole and co-workers[13] and Van Buuren and co-workers[14] were used. Final height, defined as the standing height reached when height increased less than 1·5 cm in two consecutive years of measurement; RT, radiotherapy; CI, confidence interval; n, number; [‖], interpretation of OR, by example: an OR of 2,84 in survivors treated with >300 mg/m^2 anthracyclines means that those survivors had a 2.84 higher risk to develop underweight after reaching final height compared with those treated with lower dose or no anthracyclines.

Table 4. Multilevel analysis with BMI as dependent variable after completion of cancer treatment and annual BMI change during follow-up post-treatment until reaching final height (n=299)

Variables At T=0 (by kg/m²)		Estimate	95% CI	p-value
Intercept (BMI level)		13·08	12·27 – 13·88	**<0·001**
Age at diagnosis		0·35	0·29 – 0·42	**<0·001**
Sex	Male	0		
	Female	0·21	-0·26 – 0·68	0·388
Duration of cancer treatment		0·52	0·26 – 0·79	**<0·001**
Underweight at diagnosis	No	0		
	Yes	-1·50	-2·00 – -0·99	**<0·001**
Overweight at diagnosis	No	0		
	Yes	6·19	5·14 – 7·25	**<0·001**
Anthracyclines	No	0		
	Yes	0·07	-0·44 – 0·59	0·784
Cumulative dose of anthracyclines (by 100 mg/m²)		-0·07	-0·23 – 0·09	0·383
Platin	No	0		
	Yes	0·04	-0·93 – 1·02	0·930
Any chemotherapy, no radiotherapy	No	0		
	Yes	0·19	-0·30 – 0·68	0·438
Cranial-/craniospinal irradiation	No	0		
	Yes	0·59	0·09 – 1·09	**0·020**
Chest-/neck irradiation [1]	No	0		
	Yes	-0·26	-0·84 – 0·32	0·376
Abdominal irradiation [2]	No	0		
	Yes	-0·31	-0·89 – 0·27	0·297
Total body irradiation	No	0		
	Yes	-0·96	-1·98 – 0·05	0·063
Variables **Annual BMI increase (by kg/m²/year)**		**Estimate**	**95% CI**	**p-value**
Intercept (BMI-increase)		0·47	0·34 – 0·60	**<0·001**
Age at diagnosis		0·01	-0·00 – 0·02	0·058
Sex	Male	0		
	Female	0·07	-0·01 – 0·14	0·089
Duration of cancer treatment		-0·02	-0·06 – 0·02	0·317
Underweight at diagnosis	No	0		
	Yes	-0·06	-0·14 – 0·03	0·176
Overweight at diagnosis	No	0		
	Yes	0·04	-0·13 – 0·21	0·669
Anthracyclines	No	0		
	Yes	-0·08	-0·16 – 0·003	0·058
Cumulative dose of anthracyclines (by 100 mg/m²)		-0·03	-0·05 – -0·0005	**0·046**
Platin	No	0		
	Yes	0·05	-0·11 – 0·21	0·533
Any chemotherapy, no radiotherapy	No	0		
	Yes	-0·07	-0·15 – 0·01	0·088
Cranial-/craniospinal irradiation	No	0		
	Yes	0·07	-0·01 – 0·15	0·088
Chest-/neck irradiation [1]	No	0		
	Yes	0·06	-0·04 – 0·16	0·224
Abdominal irradiation [2]	No	0		
	Yes	0·01	-0·09 – 0·10	0·880
Total body irradiation	No	0		
	Yes	0·01	-0·15 – 0·17	0·883

Note: [1], chest-/neck-irradiation was defined as radiotherapy of mantle field, mediastinum, total lung, neck and/or spine; [2], abdominal irradiation was defined as radiotherapy of abdomen, pelvic and/or spine; T=0, on completion of cancer treatment; values of intercept and independent variables 'age at diagnosis', 'sex', 'duration of cancer treatment', 'underweight at diagnosis' and 'overweight at diagnosis' were described as part of the confounder model; BMI, body mass index; underweight, BMI <18·5 kg/m²; normal weight, BMI 18·5-24·9 kg/m²; overweight, BMI ≥25·0 kg/m²; in children, BMI reference values of underweight and overweight as published by Cole and co-workers[13] and Van Buuren and co-workers[14] were used; CI, confidence interval.

21·13; 95% CI 6·40-69·78; p<0·001) and age at BMI measurement (OR 1·14; 95% CI 1·06-1·22; p<0·001). In the adjusted model (including adjustment for overweight at diagnosis), overweight after reaching final height was associated with CRT, especially if CRT dose was 30 Gy or higher. Even after adjustment for cumulative anthracycline dose >300 mg/m^2 and TBI, overweight after reaching final height was associated with CRT. (table 3)

The introduction of interaction variables between sex and the treatment modalities showed no significant difference between males and females on the effect of the treatment modalities on the prevalence of underweight and overweight after reaching final height.

BMI change post-treatment in association with previous cancer treatment (table 4 and figure 2)

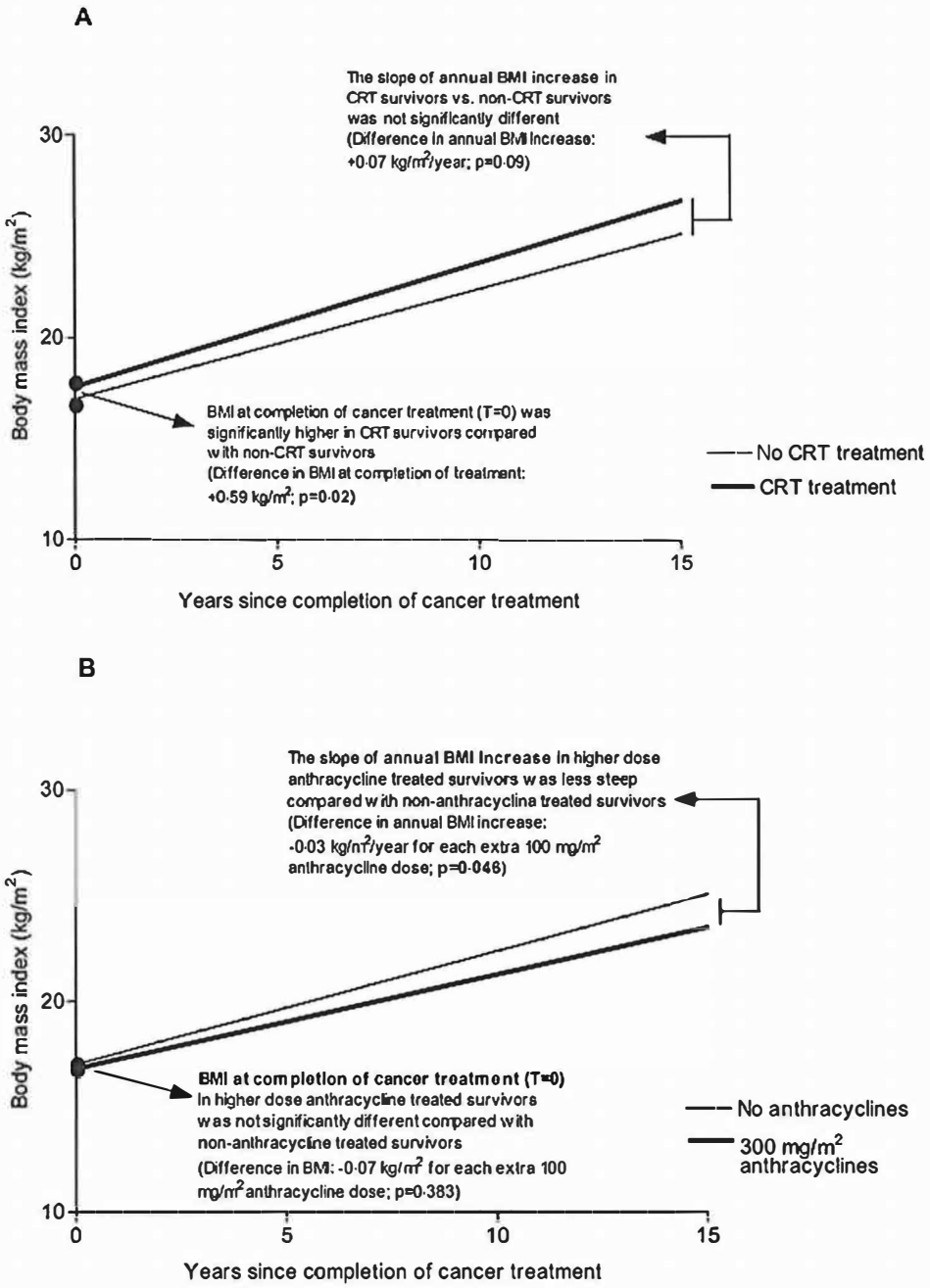
In 299/377 (79%) survivors the required number of BMI measurements before reaching final height was available (≥3 BMIs covering a follow-up period of ≥3 years). In these 299 survivors, BMI at completion of treatment and BMI increase between time of completion of cancer treatment and reaching final height were analyzed using multilevel analysis. BMI at completion of treatment was associated with age at diagnosis (Estimated BMI (Est·) +0·35 kg/m^2 for each year older at diagnosis), total duration of treatment (Est· +0·52 kg/m^2 for each extra year of treatment), underweight at diagnosis (Est· -1·50 kg/m^2) and overweight at diagnosis (Est· +6·19 kg/m^2). In a multilevel model with adjustment for these variables, BMI at completion of treatment was associated with CRT (Est. +0·59 kg/m^2; table 4; figure 2-A). TBI tended to be associated with a lower BMI at completion of cancer treatment (Est. -0·96 kg/m^2; p=0·06).

The annual BMI increase post-treatment until reaching final height was also assessed by multilevel analysis and showed an estimated BMI increase of +0·47 (0·34-060) kg/m^2/year. A slower annual BMI increase was associated with a higher cumulative anthracycline dose (Est. -0·03 kg/m^2/year for each extra 100mg/m^2; table 4; figure 2-B). Annual BMI increase for the entire group of survivors who received CRT was not significantly different compared with non-CRT survivors (p=0·09; table 4; figure 2-A). However, survivors who received a CRT dose ≥30 Gy had a higher BMI increase compared with survivors who did not receive CRT (Est. +0·15 kg/m^2/year; 95% CI 0·04-0·25; p=0·008).

DISCUSSION

The current study provides longitudinal follow-up observations of weight and height in 377 childhood cancer survivors who received potential cardiovascular toxic cancer treatment. BMI at completion of treatment was higher in survivors who received CRT, which is reflected in more overweight after reaching final height. The rate of annual BMI

Figure 2:



Note. BMI, body mass index; CRT, cranial-/craniospinal irradiation. This figure corresponds to part of the results of the multilevel analysis (table 4). The annual BMI increase after completion of cancer treatment was compared between CRT survivors and non-CRT survivors (A) and between survivors treated with 300 mg/m² anthracyclines and survivors without anthracyclines (B).

increase after completion of treatment was significantly lower in survivors who received a higher cumulative anthracycline dose, which is reflected in more underweight after reaching final height.

Although no difference in prevalence of overweight was found between the entire group of survivors and the reference population (19% vs. 22%, p=0·38), overweight after reaching final height was associated with CRT, especially if CRT dose was ≥30 Gy. This association has been reported by others in cross-sectional study designs.[6,7,18] The current study provides longitudinal BMI evaluation by assessing the rate of annual BMI increase from completion of cancer treatment until reaching final height. By combining the results of the cross-sectional and the longitudinal BMI-evaluations, we were able to describe the time course of development of under- or overweight in childhood cancer survivors. So far, only a limited number of studies have evaluated BMI at several time points during and/or after childhood cancer treatment,[7,9-12] while studies assessing the rate of BMI increase are even scarcer.[9,19] Razzouk and co-workers[9] compared the rate of BMI increase in 248 survivors of a haematological malignancy with or without CRT. They found that overweight at diagnosis was the most significant predictor of overweight at adult height, while no significantly different BMI increase over time was found among patients with or without CRT. Others found that, in particular, survivors who received >20 Gy CRT had a significantly greater net increase in BMI/year in comparison with controls; however, they did not adjust for BMI at diagnosis.[19] In our study, survivors with low-dose as well as high-dose CRT were included and we adjusted for overweight at diagnosis in the regression models. Overweight at diagnosis was found to be an important predictor of overweight after completion of cancer treatment. However, even after adjustment for overweight at diagnosis, survivors with CRT had a significantly higher BMI at completion of treatment. Survivors who received ≥30 Gy had a higher rate of BMI increase after completion of treatment until reaching final height. This may explain the higher prevalence of overweight after reaching final height in survivors who received CRT, especially in those treated with 30 Gy or more.

Thus far, little is known about underweight following cancer treatment.[8] In the current study, the prevalence of underweight after reaching final height in the entire group of survivors was higher than in the reference population (14% vs· 4%; p<0·001). Underweight at diagnosis was an important predictor of underweight after reaching final height. After adjustment for underweight at diagnosis, we found that underweight after reaching final height was associated with TBI and with a higher cumulative anthracycline dose, especially above 300 mg/m^2. These results are in accordance with those of a cross-sectional study by Meacham and co-workers.[8] They also observed a higher prevalence

of underweight in survivors compared with a national reference population (6% vs. 3%) and an association with previous treatment with anthracyclines and alkylating agents (in males and females), abdominal RT (in males) and TBI (in females).[8] In the current study, longitudinal BMI evaluation by multilevel analysis showed that BMI at completion of cancer treatment tended to be lower after TBI (p=0·06), while annual BMI increase afterwards was comparable with survivors who received no TBI. The lower BMI at completion of treatment is reflected in a higher prevalence of underweight after reaching final height in survivors who received TBI. BMI of survivors who received a higher cumulative anthracycline dose was not different at completion of treatment, whereas annual BMI increase afterwards was lower compared with those who received a lower cumulative dose or no anthracyclines. This results in more underweight after reaching final height in survivors who received a higher anthracycline dose (1·27 higher risk of underweight with each 100 mg/m^2 increase in anthracycline dose).

Both overweight and underweight have been described in association with increased all-cause mortality.[5,20] To improve existing intervention strategies in the prevention of development of abnormal body composition in childhood cancer survivors, insight into the underlying mechanisms is warranted. Various possible underlying mechanisms have been described for overweight in survivors.[21] One possible hypothesis is that overweight may be the result of a disturbed energy balance during and after childhood cancer treatment.[22,23] In survivors who received CRT, this might be caused by irradiation damage to the hypothalamic-pituitary axis.[24,25] The hypothesis of a disturbed energy balance supports our finding of a higher BMI already at completion of treatment in survivors who received CRT, suggesting that development of an abnormal body composition after CRT may start during cancer treatment.

Little is known yet about the underlying mechanisms of the development of underweight after completion of treatment with anthracyclines or TBI. Meacham and co-workers[8] stated that the majority of underweight survivors (> 70%) had an underlying problem (that is adverse health status, major medical condition and/or smoking) that contributed to their underweight. As the current study had a retrospective design, it was not possible to assess the cause-effect relationships between underweight and underlying adverse health status. Therefore, collection of longitudinal prospective data, from the start of treatment, is warranted.

Prevention of development of an abnormal body composition in survivors needs to be focused on close follow-up of weight and height, and should be started at cancer diagnosis/ treatment. Deviation from the growth curve before diagnosis may be a sign

for the development of an abnormal body composition during or after treatment. Results of the current study suggest that the type of cancer treatment may guide the timing for initiation of prevention strategies, since survivors with CRT or TBI are already at risk for an abnormal BMI during cancer treatment. In addition, a higher risk of underweight in anthracycline-treated survivors is associated with cumulative anthracycline dose and with duration of follow-up post-treatment.

The strengths of our study lie in the serial BMI data, from completion of treatment until reaching final height, in association with the prevalence of under-/overweight after reaching final height and with previous cancer treatment. One limitation is the heterogeneity of the cohort. To overcome that, we used multiple regression analyses for the adjustment of possibly confounding variables. Another limitation is that it was not possible to assess BMI change during cancer treatment because of the wide variation in duration of the treatment (range 0·1-4·9 years). To assess the exact timing and the underlying mechanism(s) in the development of abnormal body composition, prospective longitudinal evaluation of body composition is needed together with that of physical activity/energy expenditure right from cancer diagnosis/ initiation of treatment.

In conclusion, under- or overweight at diagnosis are important predictors of weight-outcome after reaching final height. However, even after adjustment for these variables, survivors after CRT had a higher BMI at completion of cancer treatment and after reaching final height, and survivors after a higher anthracycline dose had a lower BMI increase after completion of treatment, which was reflected in more underweight after reaching final height. For risk assessment in the development of abnormal body composition, health care providers and patients need to be aware of the association of CRT with overweight and anthracyclines with underweight to enable timely life-style changes.

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CHAPTER 4

Long-term cardiac follow-up in survivors of a malignant bone tumour

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Annals of Oncology 2006; 17: 1586 - 1591

ABSTRACT

Background. Longitudinal studies of cardiac function in long-term childhood cancer survivors are scarce and frequently concern a median follow-up shorter than 13 years.

Patients and methods. Cardiac assessment was performed in 22 doxorubicin-treated long-term survivors of a malignant bone tumour at median 22 years (range 15–27.5) post-treatment. Age at follow-up was 39 years (range 27–59) and cumulative dose of doxorubicin was 360 mg/m^2 (range 225–550). Cardiacfunction was assessed by echocardiography and (24-h) ECG. The results were compared with those of earlier assessments at 9 years (1992) and 14 years (1997) post-treatment.

Results. Systolic dysfunction was found in 27% (9% in 1997; $P = .02$) and diastolic dysfunction in 45% (18% in 1997; $P = .02$). Heart rate variability showed further deterioration compared with earlier results.

Conclusions. Twenty-two years after doxorubicin-treatment, bone tumour survivors showed progressive cardiac dysfunction.

INTRODUCTION

The incidence of overt heart failure in anthracycline-treated cancer survivors has been found up to 5%[1,2]. However, subclinical abnormalities in systolic and diastolic function and autonomic dysfunction may be even more frequent[3-10]. The natural course of these subclinical cardiac abnormalities remains largely unknown and it is still unclear whether or not progressive cardiac deterioration has to be anticipated.

So far only a limited number of studies on prospective longitudinal cardiac evaluation have been published, all at medium follow-up(up to 17 years)[3-6,11]. Earlier, we reported the results of longitudinal cardiac assessments in long-term doxorubicin-treated bone tumour survivors 9 and 14 years post-treatment. In this study we found no deterioration of systolic dysfunction, but a progressive reduction of heart rate variability (HRV)[12]. The aim of the current study was to re-evaluate cardiac status in the same cohort of survivors, up to 27 years post-treatment.

PATIENTS AND METHODS

Patients

The original cohort of long-term doxorubicin-treated survivors of a malignant bone tumour (osteogenic sarcoma and malignant fibrous histiocytoma), treated at the University Medical Centre Groningen, consisted of 31 patients. All patients were treated between 1977 and 1990 with combination chemotherapy according to Rosen's T5 or T10 protocol, both including doxorubicin[13,14]. Details of treatment were described earlier[12,15]. Patients had assessment of cardiac function at median 9 years post-treatment in 1992 (n = 31), at 14 years post-treatment in 1997 (n = 29) and at 22 years post-treatment in 2004 (n = 22). Reasons for non-participation in 1992 or 1997 were death from congestive heart failure (n = 1), death from second malignancy (n = 1), thoracic irradiation for second malignancy and hence exclusion (n = 2; both patients were also known with cardiomyopathy), terminal neurodegenerative disease (n = 1) and refusal (n = 4). Characteristics of the 22 remaining patients are summarised in Table 1. The study protocol was approved by the Ethics Committee of the University Medical Centre Groningen. Written informed consent was obtained from all patients and controls.

Measurements

The evaluation consisted of a medical history, physical examination, Doppler echocardiography, fasting blood sample, 12-lead electrocardiograph (ECG) and 24-h ambulatory ECG.

Table 1. Characteristics of the 22 participants in 2004

Male/ female	17 / 5
Age (years) at start of chemotherapy	
Median	17
Range	10 – 38
Age (years) at follow-up	
Median	39
Range	27 – 59
Follow-up period (years)	
Median	22
Range	15.0 – 27.5
Doxorubicin cumulative dose (mg/m^2)	
Median	360
Range	225 – 550

Blood pressure was measured twice on both arms in supine position in a quiet room after a minimal rest period of 10 min and compared with age- and sex matched controls (40 males, 12 females; median age 40 years, range 26–55). Criteria for hypertension were systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or treatment with antihypertensiva.

Echocardiography was performed by a single skilled technician on a General Electric VIVID 7 system with a 2.5 mHz probe and consisted of two-dimensional echocardiography, colour flow mapping and 2D-guided M-mode, blood pool and tissue Doppler echocardiography[16]. Systolic function was measured by shortening fraction (SF) and wall motion score index (WMSI). Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) and end-diastolic left ventricular posterior wall thickness (LVPWed) were measured on M-mode recordings obtained in the standard left ventricular parasternal long axis view. SF was calculated with the formula: (LVEDD-LVESD)/ LVEDD x 100%. A SF <29% was considered abnormal. The normal range for LVEDD is 36–54 mm, for LVESD 23–40 mm and for LVPWed 7–11 mm. For the regional analysis of left ventricle systolic function, the left ventricle was divided into 16 segments. Each segment was visually scored between 0 and 4 (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia). WMSI was derived by adding the scores assigned to each segment and dividing the total score with the number of analysed segments. WMSI of 1.00 was considered normal and to correlate with a left ventricular ejection fraction >60%. WMSI >1.50 indicates a significant systolic dysfunction. Diastolic function measurements included mitral valve inflow velocities in early (E) and late (A) diastole and diastolic tissue velocity at the mitral valve annulus [Tissue Velocity Imaging of early diastole (TVI Et)]. E/A

ratio <1.00 was considered abnormal and may represent diastolic dysfunction. A mean TVI Et <8.0 cm/s was considered diastolic dysfunction[17].
A standard 12-lead ECG was recorded and analysed by a single observer for flattened T-waves, pathological Q-waves or a prolonged QTc. T-waves were characterised as abnormal flattened if three or more precordial leads and three or more standard leads had an amplitude less than +2 or −2 mm. In males QTc >0.44 s was considered abnormal and in females QTc >0.46 s.

The 24-h ambulatory ECG was analysed on a GE Marquette Holter system by an experienced Holteranalyst. All Holters were analysed for rhythm and conduction disturbances. Ventricular arrhythmias were classified according to the Lown's criteria[18]. Lown 4 or higher was considered abnormal.

For analysis of HRV, data were transformed to a PC and custom made software (COHWIN) was used to analyse HRV [19]. Both time domain, as well as frequency domain parameters, were calculated in accordance with the recommendations for analysis of HRV[20]. For frequency domain parameters 5 min segments were used. Segments containing more than 10% ectopics as well as non-stationary segments were excluded from the analysis. We determined the spectral power over three frequency regions of interest: LF, low frequency power (0.04–0.15 Hz); HF, high frequency power (0.15–0.4 Hz); and TP, total power (0.01–1.00 Hz). In particular the parameters rMSSD (root mean square of successive difference) and HF reflect parasympathetic activity. HRV is heart rate- and, therefore, gender- and age-dependent[19]. Therefore, we compared all measurements with sex- and age-matched controls, recruited from a group of 419 healthy subjects, who were investigated previously[19]. For comparison of HRV parameters measured in 1997 and 2004, we used two separate control groups. The first control group was matched with the age of the survivors in 1997 and the second control group with the age of the survivors in 2004. Furthermore, the HRV parameters measured in 1997 were reanalysed by the same software used in 2004 and compared with the HRV measurements in 2004.

Statistical analysis

Statistical analyses were performed in SPSS inc. version 12 by the non-parametric Mann–Whitney, Friedman, Wilcoxon's and chi-square tests. Because of the small sample size and the non-Gaussian distribution of the different parameters non-parametric tests were used. Data were reported as median (range). Two-sided *P* values $\leq .05$ were considered significant.

RESULTS

Clinical parameters

One patient complained of dyspnoea on effort. She had medication for left ventricular dysfunction (ACE inhibitor, Captopril®), which was initiated 7 years earlier at 17 years post-treatment. None of the other patients had cardiac symptoms.

Blood pressure

Eight out of 22 patients (36%) had hypertension: five had systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and three were on antihypertensive medication. Hypertension was equally frequent in controls [14/52 (27%)]. Systolic blood pressure was 121 (range 102–178) mmHg versus 126 (range 96–150) mmHg in controls

Table 2. Cardiac dysfunction and hypertension in long-term survivors of a malignant bone tumour (n = 22)

Patient	Sex	Age	Systolic dysfunction (SF < 29%)			Diastolic dysfunction (E/A < 1.00 and/or TVI Et <8.0 cm/sec			Hypertension in 2004
			1992*	1997*	2004	1997 E/A*	2004 E/A	2004 TVI Et	
1	M	56	-	-	-	+	+	+	-
2	M	39	-	-	-	-	+	-	-
3	F	37	-	-	-	-	-	-	-
4	M	44	-	-	+	+	+	+	+
5	F	42	-	-	-	-	-	-	-
6	M	42	+	-	-	-	-	-	-
7	F	48	+	+	+	-	+	+	+
8	M	58	-	-	-	-	-	+	-
9	M	38	-	-	-	-	+	+	-
10	M	47	-	-	-	-	+	-	-
11	M	33	+	-	-	-	-	-	-
12	M	39	-	-	-	-	-	+	-
13	M	44	-	-	+	+	+	+	+
14	M	30	-	-	-	-	-	-	-
15	F	59	-	+	+	+	+	+	-
16	M	38	+	-	-	-	-	-	-
17	M	37	-	-	-	-	-	-	+
18	M	42	-	-	-	-	-	-	+
19	M	27	-	-	+	-	-	+	-
20	M	34	-	-	-	-	+	+	-
21	F	30	-	-	-	-	-	-	-
22	M	36	-	-	+	-	+	+	+
Total			4	2	6	4	10	11	6

Note: M, male; F, female; yrs, years; E, peak early phase velocity; A, peak atrial phase velocity; TVI Et, Tissue Velocity Imaging; SF, shortening fractioning; +, yes; -, no. * Data from earlier studies [12,15]

(not significant, NS). Diastolic blood pressure was 80 (range 70–120) mmHg versus 80 (range 59–106) mmHg in controls (NS).

Echocardiography

The results of echocardiography are summarised in Tables 2 and 3. Six out of 22 patients (27%) had decreased SF, compared with two out of 22 in 1997 ($P = .015$). All six patients with decreased SF also had an abnormal WMSI: four of six had a diffuse wall motion abnormality and two of six had a regional wall motion abnormality. One of these six patients was already known with left ventricular dilatation and systolic dysfunction diagnosed earlier. In the other five patients, systolic dysfunction was a novel finding.

Ten of 22 patients had abnormal E/A ratio compared with four of 22 in 1997 ($P = .02$). Median E/A ratio decreased significantly (1.05 in 2004 versus 1.31 in 1997, $P < .001$). TVI Et (not measured in the earlier studies) was abnormal in 11/22 patients (50%). Taking E/A ratio as well as TVI Et into account, 13/22 patients (59%) had diastolic dysfunction (E/A ratio <1.00 and/or TVI Et <8.0 cm/s), including all six patients with systolic dysfunction (Table 2).

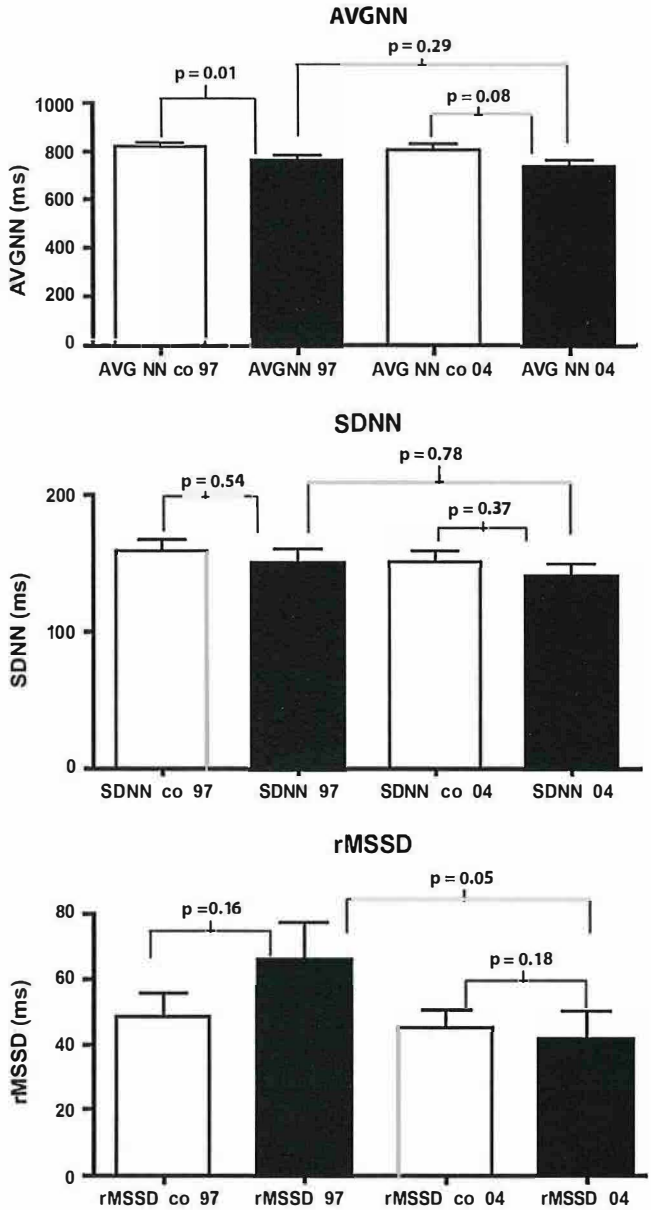
Median LVEDD was 49.5 (range 41–56) mm versus 52 (43–58) mm in 1997 ($P = .007$). Median LVESD was 33 (23–43) mm versus 35 (31–41) mm in 1997 ($P = .004$). Median LVPWed was 9 (6–12) mm versus 8 (7–10) in 1997 ($P = .02$). LVEDD was enlarged in two of 22 patients and LVESD was enlarged in one of 22 patients. LVPWed was abnormally thick in two of 22 patients and too thin in one of 22 patients.

Table 3. Summary of the cardiac abnormalities in six patients with systolic dysfunction

Patient	Sex	Age in 2004	FU	Cum dose Doxo	SF	WMSI	Local or diffuse WMA	E/A	Abnormal Q-waves at ECG?
		yrs	yrs	mg/m^2	%				
1	M	44	17	300	23.2	1.25	Local	0.77	Yes
2	F	48	21	240	24.5	1.68	Diffuse	0.74	Yes
3	M	44	26	550	25.0	1.13	Diffuse	0.53	Yes
4	F	59	25	360	26.4	2.00	Diffuse	0.70	No
5	M	27	18	360	28.8	1.12	Local	1.15	No
6	M	36	19	450	25.9	1.81	Diffuse	0.61	No

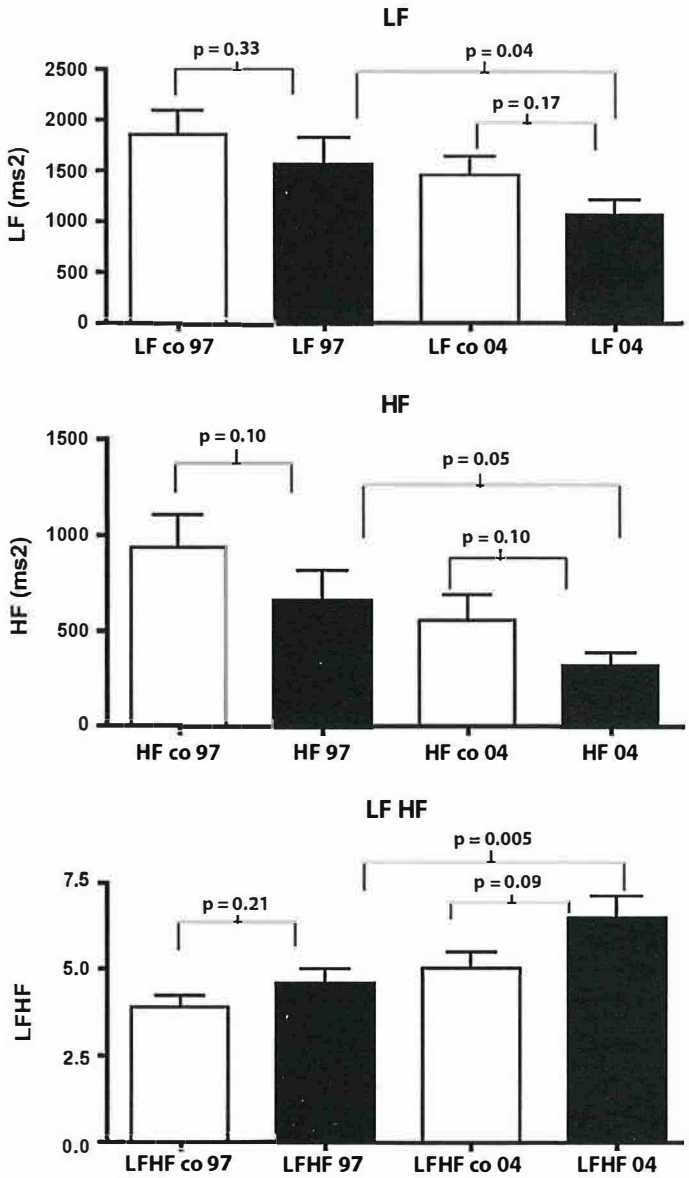
Note: M, male; F, female; FUP, follow-up period; yrs, years; cum dose Doxo, cumulative dose of doxorubicin (in mg/m^2); SF, shortening fractioning; WMSI, wall motion score index; WMA, wall motion abnormality; E, peak early phase velocity; A, peak atrial phase velocity; ECG, electrocardiograph.

Figure 1. Time domain parameters



Note: AVGNN, average of all NN-intervals (ms); SDNN, standard deviation of all NN-intervals (ms); rMSSD, root mean square of successive difference (ms); Co, controls; 97, Holter analysis in 1997; 04, Holter analysis in 2004; statistical analyses by non-parametric tests (Wilcoxon's test for paired comparison between parameters measured in patients in 1997 and in 2004 and Mann–Whitney's test for comparison parameters measured in patients and in controls), *P* value $\leq$ .05, statistical significant; use of two different control groups, sex- and age-matched with the age of the survivors in 1997 and 2004.

Figure 2. Frequency domain parameters



Note: LF, low frequency power (ms²); HF, high frequency power (ms²); LFHF, LF/HF. Co, controls; 97, Holter analysis in 1997; 04, Holter analysis in 2004; statistical analyses by non-parametric tests (Wilcoxon's test for paired comparison between parameters measured in patients in 1997 and in 2004 and Mann–Whitney's test for comparison parameters measured in patients and in controls), *P* value ≤ .05, statistical significant; use of two different control groups, sex- and age-matched with the age of the survivors in 1997 and 2004.

We found no correlation between SF, WMSI or E/A ratio and cumulative dose of doxorubicin, age at diagnosis, current age or follow-up.

ECG

Twelve-lead ECG was performed in 21 of the 22 patients. One patient had a prolonged QTc (0.46 s), although his previous ECG recordings were normal. Four of the 21 patients had abnormal Q-waves: three of them also had systolic dysfunction measured as SF <29% (Table 3). Nine of 21 patients (43%) had T-wave flattening versus five of 22 in 1997 (P = .003).

In the current study 21/22 patients received 24-h ECG. One patient, who was already known with ventricular couplets (Lown 4) and non-sustained supraventricular tachycardia (SVT), refused the registration. Median heart rate of the 21 patients was 85 (62–99)/min. One patient, who was already known with second-degree Wenckebach atrio-ventricular (AV) block at night, had a third-degree AV-block at night at the current 24-h ECG. Five of 21 patients had sporadic (less than 100/24 h) premature ventricular contractions (PVCs) (Lown 1), seven of 21 had multiform PVCs (Lown 3) and one of 21 had ventricular couplets (Lown 4). None of the patients showed (non-) sustained (supra) ventricular tachycardia[18].

HRV was evaluable in 19/22 patients. HRV results were compared with age-matched controls and also with the individual earlier HRV analysis of 1997. Compared with age-matched controls, patients showed lower values of HRV parameters, except for LF/HF and LFNU (normalised unit of LF). LnTP (natural logarithm of TP) was significantly lower in patients compared with controls (P = .041). Therefore, HRV measurements indicate sympathetic dominance in the patient group. Almost all HRV parameters decreased compared with the measurements in 1997, some of them significantly. Low frequency parameters, as LF/HF and LFNU, increased (Figure 1-2).

DISCUSSION

In this longitudinal study we found progressive impairment of systolic and diastolic function and of HRV in doxorubicin-treated bone tumour survivors after a very long follow-up period (up to 27 years). Forty-five per cent of the 22 long-term survivors (median age 39 years) had diastolic dysfunction and 27% had systolic dysfunction. Furthermore, three of the nine patients who did not participate in the current evaluation were already known with cardiac dysfunction.

Although in our previous study systolic dysfunction, measured as SF, did not progressively decrease in 9–14 years follow-up, the number of patients with abnormal SF increased

significantly in this extended follow-up study. All six patients with impaired SF at the current assessment also had an elevated WMSI. Four of them had diffuse wall motion abnormalities and two had regional wall motion abnormalities, suggesting ischaemic heart disease (confirmed in one of them by positron emission tomography).

The results of longitudinal echocardiography in moderate term anthracycline-treated cancer survivors have been somewhat conflicting: some studies showing ongoing progression of abnormalities, others showing no further deterioration[3-6,11]. Lipshultz et al[6] showed a significantly depressed SF shortly after doxorubicin therapy, improvement 6 years post-treatment, but progressive impairment of SF 12 years post-treatment. This is in accordance with the results of our study, as we also found unchanged SF at moderate term follow-up and subsequently a further decrease. However, compared with other studies including that of Lipshultz et al, our follow-up was considerably longer: 22 years compared with about 13 years in most other studies[3-6,11].

Although the median dimensions decreased significantly compared with earlier measurements, LVEDD and LVESD remained within normal limits. This is in accordance with the results of Lipshultz et al [6], who found normal left ventricular dimensions after cessation of therapy and no further deterioration up to 12 years post-treatment.
At 22 years follow-up we found impairment of diastolic function, measured as E/A ratio, in 45% of the patients. This is in contrast with the findings of Bossi et al, who found no diastolic dysfunction in childhood cancer survivors treated with 214 mg/m^2 doxorubicin and/or daunorubicin[7]. However, our patients received a much higher dose of doxorubicin (median cumulative dose 360 versus 214 mg/m^2 in Bossi's study) and our follow-up was much longer (22 versus 7 years). Therefore our results suggest that the prevalence of diastolic dysfunction increases with a longer follow-up period. Dorup et al[21] stated that diastolic dysfunction cannot be described by one index only, but depends on an interaction between several parameters. An interesting new parameter to detect diastolic function is TVI Et, because it is independent of left ventricular filling (load independent)[16,21]. As far as we know, our study is the first cardiac study in long-term cancer survivors that used TVI Et for measurement of diastolic function. If we consider TVI Et as a parameter of diastolic function, the number of patients with diastolic dysfunction in our study group is even higher (13/22; 59%).

We found no relation between cardiac abnormalities and cumulative dose of doxorubicin, probably because all patients had moderate or high doses of doxorubicin (range 225–550 mg/m^2) and no patient had been treated with lower doses of doxorubicin.

Compared with an age-matched control group, all HRV variables pointed in the same direction: a shift towards sympathetic domination (Figure 1-2). Compared with age-matched controls, none of the HRV variables measured in 2004 showed a statistical difference with the accessory age-matched control group. On the other hand, comparing HRV variables measured in 2004 with variables measured in 1997, a statistical decrease in frequency domain parameters was found (Figure 2). Part of the decrease in HRV variables can probably be explained by the age-related decrease of HRV[19]. A cause for the non-significance for several of the HRV parameters could be the small sample of patients (n = 22). Our findings, for example a decreased HRV in combination with diastolic and systolic dysfunction at echocardiography, are in accordance with those of other authors, who found heart failure (either clinical or subclinical) to be associated with a decrease in HRV[22-24].

Our study has some limitations. First, the small number of patients may have compromised statistical evaluation. Secondly, patients reported no cardiac symptoms, but this was not confirmed by exercise tests. Finally, the results of the current study are not completely comparable with those of the previous ones. In the current study we used WMSI and TVI Et to determine cardiacfunction. These techniques are superior to those used in the previous studies, but were not available at that time.

In conclusion, longitudinal assessment of cardiac function in anthracycline-treated survivors of a malignant bone tumour showed a high rate of systolic and diastolic dysfunction (27% and 45%, respectively). Moreover, cardiac dysfunction was progressive in 9–22 years follow-up. Our results suggest that after treatment with anthracyclines there is an ongoing deterioration of cardiac function and no extinction is anticipated. Therefore, anthracycline-treated cancer survivors are considered for life-long cardiac surveillance.

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CHAPTER 5

Low-dose anthracyclines in childhood Acute Lymphoblastic Leukemia (ALL): no cardiac deterioration more than 20 years post-treatment

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Journal of Cancer Survivorship 2007; 1: 255 - 260

ABSTRACT

Introduction. In children with cancer a well-known risk factor for cardiotoxicity is a high cumulative dose of anthracyclines, but little is known about cardiac function in low-dose anthracycline-treated survivors. Also, it is unclear if a safe anthracycline-dose exists at all.

Patients and methods. Cardiac function was assessed in 23 long-term ALL-survivors with a median follow-up of 22 years (range 19.5–24.5) post-treatment. Age at diagnosis and current age were 5.0 (2.0–14.0) and 29.0 (24.0–39.0) years. All 23 survivors were treated according to DCLSG protocol ALL-5, including 18–25 Gy cranial irradiation. Thirteen of them received 4 x 25 mg/m^2 daunorubicin by randomization. Cardiac evaluation included blood pressure measurement, echocardiography, and (24 h-) electrocardiogram. Results were compared with an earlier assessment at median 12 years post-treatment.

Results. None of the survivors had cardiac abnormalities. Cardiac status of daunorubicin-treated survivors showed no deterioration compared with the previous assessment in 1995.

Conclusion and implication for cancer survivors. After prolonged follow-up (more than 20 years post-treatment), ALL-survivors treated with low dose daunorubicin had no clinical relevant deterioration of cardiac function.

INTRODUCTION

During the last few decades, efficacy of childhood cancer treatment improved substantially, which led to an increase in survival of childhood cancer patients. This increased survival is partly due to the introduction of the anthracyclines in the 1970s. Although very effective anti-cancer drugs, anthracyclines may cause cardiac dysfunction[1-3]. The cumulative risk of developing clinical heart failure more than 20 years after anthracycline-treatment has been reported to be 5.5%[1]. Prevalence of subclinical heart failure was even found in up to 57%[4]. The risk of developing heart failure after anthracycline-treatment seems to be dose-dependent[5]. At a median follow-up of 7.1 years after the first dose of anthracyclines, a recent study showed that survivors treated with less than 150 mg/m^2 anthracyclines [i.e. doxorubicin, daunorubicin (DNR), epirubicin and/or idarubicin] had no risk for developing clinical heart failure, while survivors treated with more than 600 mg/m^2 had a risk of 14.3%.[1] To determine the possible late development of (sub)clinical cardiac dysfunction in low-dose anthracycline-treated survivors, longitudinal studies with a more prolonged follow-up are warranted.

Earlier, we reported the results of a cross-sectional, nationwide, multi-center cardiac study in 90 long-term survivors of acute lymphoblastic leukemia (ALL) who were randomized to receive low dose anthracyclines in the induction phase (four weekly doses of 25 mg/m^2 DNR)[6]. Fifty of these 90 survivors received the low dose of DNR and 40 were treated without DNR. No deterioration of cardiac function and heart rate variability (HRV) was found in the DNR-treated survivors compared with the non-DNR-treated ones. The current study re-assesses cardiac status at a very long follow-up of median 22 years post-treatment in a subset of the earlier studied survivors, namely in those who were treated at a single institution (n = 28).

PATIENTS AND METHODS

Patients

The initial cohort of survivors treated for childhood ALL at the University Medical Centre Groningen between 1978 and 1984 and participating in a nationwide, multi-center cardiac study in 1995, consisted of 28 patients. All patients were treated according to the DCLSG (Dutch Childhood Leukaemia Study Group) ALL-5 protocol with or without DNR. Furthermore, all patients received a dose of 18 to 25 Gy cranial irradiation as central nervous system prophylaxis. Details about the ALL-5 protocol were described earlier and are summarized in Table 1[6].

In 1995, 28 institutional ALL-survivors had an assessment of cardiac function at 12 (range, 10.5–15.0) years post-treatment. In 2005, 23 of them were re-assessed 22 (19.5–24.5) years

Table 1. DCLSG ALL5 protocol – outline

Induction treatment	
Duration: 6 weeks	• Vincristin 6x2mg/m²/wk • Prednisone 28x40 mg/m²/day • L-Asparaginase 14x200E/kg/day in week 4-6 • **Randomisation:** with or without 4x25mg/m²/wk Daunorubicin
Central nervous system prophylaxis	
Duration: 2.5 –3 weeks	• Cranial irradiation 18 - 25 Gy • Methotrexate 12,5 mg/m² (maximum 15 mg/dose) and Prednisone 12,5 mg/m² 5x intrathecally
Maintenance & consolidation phase	
Duration: Until 2 years from start of treatment	Five weeks 6-Mercaptopurine 50 mg/m²/day and Methotrexate 30 mg/m²/wk, alternating with two weeks Vincristin 2 mg/m²/wk and Prednisone 40 mg/m²/day

Note: DCLSG, Dutch Childhood Leukemia Study Group

post-treatment. Reasons for non-participation in 2005 were second malignancy (n = 1) and refusal (n = 4). As far as we know, these non-participating survivors had no (clinical) signs of cardiac failure. Characteristics of the 23 participating survivors are summarized in Table 2. Because of randomization during the induction phase of the DCLSG ALL-5 protocol, 13 of the 23 survivors received treatment with four weekly doses of 25 mg/m² DNR (DNR+ group), while the others (n = 10) received no DNR during the induction phase (DNR- group). The study protocol was approved by the Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all patients.

Measurements

Cardiac evaluation consisted of a medical history, full physical examination, blood pressure measurement, Doppler echocardiogram, 12-lead electrocardiogram (ECG) and 24-h ambulatory ECG (24-h ECG).

Standardized measurements of blood pressure were performed in a quiet room in the supine position. Blood pressure was measured twice on the left arm and the lowest blood pressure measurement was taken for analysis. Criteria of hypertension were systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or treatment with antihypertensive drugs. Blood pressure measurements at the current assessment were compared with the results of 1995.

Table 2. Characteristics of the participants

	Total (n = 23)	DNR+ (n = 13)	DNR- (n = 10)
Gender			
Male/ female	9/14	6/7	3/7
Age (years) at diagnosis			
Median (range)	5.0 (2.0 – 14.0)	5.0 (2.0 – 14.0)	5.0 (2.0 – 12.0)
Age (years) at follow-up			
Median (range)	29.0 (24.0 – 39.0)	30.0 (24.0 – 39.0)	27.5 (26.0 – 34.0)
Follow-up period (years)			
Median (range)	21.5 (19.5 – 24.5)	22.0 (20.0 – 24.5)	20.8 (19.5 – 23.5)

Note: No significant differences in sex, age at diagnosis, age at follow-up, follow-up period and dose of cranial irradiation between daunorubicin-treated survivors and non-daunorubicin-treated survivors. DNR+, treated with 4 x 25 mg/m^2 daunorubicin; DNR-, treated without daunorubicin

Echocardiography was performed in order to determine systolic and diastolic function. A single skilled technician performed echocardiography on a General Electric VIVID 7 system with a 2.5 mHz probe. Echocardiography consisted of two-dimensional echocardiogram, color flow mapping and 2D-guided M-mode, blood pool, and tissue Doppler echocardiogram [7]. We measured left ventricular end-diastolic dimension (LVEDD; normal 36–54 mm), left ventricular end-systolic dimension (LVESD; normal 23–40 mm), intraventricular septum end-diastolic (IVSed; normal 7–11 mm), and end-diastolic left ventricular posterior wall thickness (LVPWed; normal 7–11 mm) in the M-mode, obtained in the standard left ventricular parasternal long axis. Shortening fraction (SF) and wall motion score index (WMSI) were indicators of systolic function. SF was calculated with the formula: (LVEDD-LVESD)/LVEDD x 100%. WMSI was calculated by visually scoring between 1 and 4 of each of the 16 segments of the left ventricle (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 =dyskinesia). The scores of each segment were added and the total score was divided by the number of analysed segments. A SF above 29% and a WMSI of 1.00 are considered to be normal. Diastolic function measurements included mitral valve inflow velocities [early (E) as well as late (A) in diastole] and diastolic tissue velocity at the mitral valve annulus [tissue velocity imaging of early diastole (TVI Et); parameter of diastolic function independent of left ventricular filling]. E/A ratio <1.00 was considered abnormal and may represent diastolic dysfunction. A mean TVI Et <8.0 cm/s was considered diastolic dysfunction [8].

A standard 12-lead ECG was recorded and analysed by a single observer for flattened T-waves, pathological Q-waves or a prolonged QTc. T-waves were characterised as flattened if three or more precordial leads and three or more standard leads had an amplitude less than +2 or -2 mm. In males QTc >0.44 s was considered abnormal and in females QTc >0.46 s.

The 24-h ECG was analysed on a GE Marquette Holter system by an experienced Holteranalyst. All Holters were analysed for rhythm and conduction disturbances. Ventricular arrhythmias were classified according to the Lown's criteria [9]. Lown 4 or higher was considered abnormal.

For analysis of HRV, data were transformed to a PC and custom made software (COHWIN) was used to analyse HRV[10]. Both time domain and frequency domain parameters were calculated in accordance with the recommendations for analysis of HRV[11]. For frequency domain parameters 5 min segments were used. Segments containing more than 10% ectopics as well as non-stationary segments were excluded from the analysis. We determined the spectral power over three frequency regions of interest: LF, low frequency power (0.04–0.15 Hz); HF, high frequency power (0.15–0.4 Hz); and TP, total power (0.01–1.00 Hz). In particular the parameters rMSSD (root mean square of successive difference) and HF reflect parasympathetic activity. HRV is heart rate-, and therefore, gender- and age-dependent[10]. In 1995 no abnormalities in HRV were found [6]. Therefore, we only compared HRV measurements of 2005 with sex- and age-matched controls (n = 23), recruited from a group of 419 healthy subjects, who were investigated previously[10].

Statistical analyses

Statistical analyses were performed in SPSS Inc. version 12 by the non-parametric Mann–Whitney, Wilcoxon's, Chi squared and McNemar tests. Data were reported as median (range). Two-sided *P* values ≤ .05 were considered significant.

RESULTS

Clinical parameters and physical examination

No significant differences in sex, age at diagnosis, age at follow-up and follow-up period were found between DNR+ survivors and DNR- survivors (Table 2). Furthermore, there was no difference in dose of cranial irradiation between both groups. DNR+ survivors as well as DNR- survivors received median 25 (range, 18–25) Gy cranial irradiation. Three of the 13 DNR+ ALL-survivors complained of palpitations and one of dyspnoea with exertion, while none of the DNR- ALL-survivors had cardiac symptoms.

At the current assessment, the entire group of ALL-survivors did not have a higher prevalence of hypertension compared with 1995 ($P = 1.00$). Furthermore, no differences in prevalence of hypertension were found between DNR+ and DNR- survivors ($P = .56$) and DNR+ survivors as well as DNR- survivors had no higher prevalence of hypertension in 2005 compared with 1995 ($P = 1.00$; Table 3).

Echocardiography

The results of echocardiography are summarized in Table 3. All ALL-survivors, DNR+ as well as DNR-, showed normal systolic function (all survivors had a SF >29% and a WMSI of 1.00). Median SF was higher in 2005 compared with 1995 ($P = .03$). Only one of the ALL-survivors,

Table 3. Results of physical examination and echocardiography

	ALL-survivors in 1995 (n = 23)			ALL-survivors in 2005 (n = 23)		
	All survivors	**DNR+**	**DNR-**	**All survivors**	**DNR+**	**DNR-**
	(n=23)	*(n=13)*	*(n=10)*	*(n=23)*	*(n=13)*	*(n=10)*
Hypertension (Blood pressure ≥140/90mmHg)	2/23 (9%)	1/13 (8%)	1/10 (10%)	3/23 (13%)	1/13 (8%)	2/10 (20%)
SF (%)[1]	34 (31-39)	33 (31-39)	35 (32-38)	36[¥] (29-52)	36 (29-52)	37 (33-44)
E/A ratio[1]	1.8 (1.1-2.9)	1.9 (1.4-2.9)	1.8 (1.1-2.4)	1.7 (0.8-2.4)	1.7[†] (1.3-2.4)	1.7 (0.8-2.4)
IVSed (mm)[1]	9.0 (8-12)	9.0 (8-11)	9.0 (8-12)	8.0[§] (6-11)	8.0[¶] (6-9)	8.5 (7-11)
LVPWed (mm)[1]	9.0 (7-10)	9.0 (7-10)	9.0 (7-10)	8.0 (5-10)	8.0 (5-10)	8.0 (6-10)
LVESD (mm)[1]	30.0 (25-36)	30.0 (25-36)	30.5 (26-33)	29.0* (22-34)	29.0 (22-34)	29.0 (22-33)
LVEDD (mm)[1]	46.0 (41-53)	46.0 (41-53)	46.0 (41-51)	46.0 (39-51)	47.0 (40-51)	45.5 (39-49)

Note: ALL, acute lymphoblastic leukaemia; DNR+, treated with 4x25 mg/m^2 daunorubicin (DNR); DNR-, treated without DNR; SF, shortening fraction; IVSed, intraventricular septum end-diastolic; LVPWed, end-diastolic left ventricular posterior wall thickness; LVESD, left ventricle systolic diameter; LVEDD, left ventricle end-diastolic diameter;. [1], median (range); ¥, $P = .03$, comparison of SF between 1995 and 2005 of all survivors; †, $P = .02$, comparison of E/A ratio between 1995 and 2005 in survivors treated with DNR; §, $P = .001$, comparison of IVSed between 1995 and 2005 in all survivors; ¶, $P = .004$, comparison of IVSed between 1995 and 2005 in survivors treated with DNR; *, $P = .02$, comparison of LVESD between 1995 and 2005 in all survivors

treated without DNR, showed diastolic dysfunction. This was a 31-year-old woman with an E/A ratio of 0.84 and a mean TVI Et of 6.0 cm/s and with a mildly elevated blood pressure (137/92). For the whole group of ALL-survivors diastolic function (measured as E/A ratio) tended to decrease compared with 1995 ($P = .06$). Furthermore, compared with 1995, we found a decreased IVSed ($P = .001$), a decreased LVESD ($P = .02$) and LVPWed tended to be thinner ($P = .06$). However, at the assessment of 2005, all survivors had a IVSed, LVPWed, LVEDD and LVESD within normal range, except for one DNR+ survivor with a decreased IVSed (6 mm) and LVPWed (5 mm) and for one DNR- survivor with a decreased LVPWed (6 mm). At the assessments of 1995 and 2005, no differences were found in cardiac parameters between DNR+ and DNR- ALL-survivors.

In the DNR+ survivors, E/A-ratio decreased significantly compared with 1995 ($P = .02$), although all values were still within normal limits. The decline in E/A ratio in the DNR+ survivors was not significantly different from the decline in the DNR- group ($P = .11$). In addition, mean TVI Et (only measured in the cardiac assessment of 2005) showed no difference in TVI Et between DNR+ and DNR- survivors [10.9 (9.0–12.9) vs. 10.2 (6.0–12.6) cm/s, $P = .42$]. In the DNR+ survivors, the IVSed decreased compared with 1995 ($P = .004$). The decline in IVSed in the DNR+ survivors was not significantly different from the decline in the DNR- group ($P = .65$). Furthermore, LVPWed and LVESD tended to decrease, however, not significantly ($P = .08$, respectively, $P = .09$). No significant differences were found in SF and LVEDD ($P \geq .10$; Table 3). In the DNR- survivors, IVSed tended to decrease ($P = .06$), while SF, E/A-ratio, LVPWed, LVESD and LVEDD showed no significant differences between 2005 and 1995 ($P \geq .10$).

(24-h) ECG

In 2005, 12-lead ECG showed flattened T-waves in 7/23 (30%) survivors. DNR+ survivors had no more often abnormal flattened T-waves compared with DNR- survivors ($P = 1.00$). None of the survivors had pathological Q-waves or a prolonged QTc.

All survivors underwent 24-h ECG. Median (range) heart rate of the survivors was 76 (67–88)/min. All survivors had sinus rhythm on their ECGs with normal atrioventricular conduction. One DNR+ survivor had sporadic (less than 100/24 h) premature ventricular contractions (Lown 1) and two DNR- survivors had ventricular couplets (Lown 4). None of the survivors showed sustained (supra) ventricular tachycardia. At the earlier assessment in 1995, two survivors had Lown 1, one Lown 2 and one Lown 4.

HRV was evaluable in all survivors and the results were compared with age- and sex-matched controls (n = 23). No abnormalities in HRV were found. All time and frequency

domain parameters were comparable with those of the controls, except rMSSD (time domain parameter). The rMSSD was higher in patients compared with controls [median (range) 54.0 ms (26.8–217.4) vs. 37.7 ms (16.2–102.3); $P = .02$]. Furthermore, no significant differences in time and frequency domain parameters were found between DNR+ and DNR- survivors. Also at the cardiac assessment of 1995, no abnormalities in HRV were found.

DISCUSSION

In this longitudinal cardiac study with an extended follow-up, we found no deterioration of cardiac function and no signs of autonomic dysfunction in ALL-survivors irrespective of their treatment with DNR.

Until now, longitudinal cardiac studies in childhood cancer survivors are scarce, especially those with an extended follow-up period. Recently, we published the results of a cardiac follow-up study in bone tumor survivors and found progressive cardiac dysfunction more than 20 years post-treatment[12]. All these survivors had been treated with medium to high dose of anthracyclines. Even less is known about the very long-term follow-up in survivors treated with low-dose of anthracyclines. Lipshultz et al found that, at median 12 years post-treatment, SF was relatively normal in the low-dose group [n = 25; less than 300 mg/m^2 doxorubicin; mean *z* score of SF -0.59 (-1.78 to 0.61)]. However, they stated that even patients who received a cumulative dose as low as 45 mg/m^2 doxorubicin (n = 18), eventually experienced cardiac abnormalities, such as significantly reduced left ventricular mass and dimension [2]. A dose-related effect of subclinical cardiotoxicity was found in other studies [5,13]. A recent cross-sectional study [with a median follow-up of 7.1 years (range 0.01–28.4)] demonstrated no clinical heart failure in survivors who had been treated with less than 150 mg/m^2 anthracyclines [1]. In this study, data were collected from medical records and questionnaires (filled out by the general practitioners of the survivors). The results of the present study support the finding that low-dose DNR might be safe, as we found neither clinical nor subclinical cardiac abnormalities after a much longer follow-up of 22 years post-treatment.

Compared with the first cardiac assessment in 1995, we found a decrease in E/A-ratio in the DNR+ survivors (n = 13), although all measurements were within normal limits. As the recent cardiac assessment of 2005 was about 10 years after the first one, the decrease in E/A ratio can be considered age-related. This is in accordance with Spirito et al [14] who described the age-related decline of E/A ratio. In addition, no significant difference in the decline in E/A ratio was found between DNR+ survivors and DNR- survivors and mean TVI Et, measured in 2005, was not different between DNR+ and DNR- survivors. This makes a

cardiotoxic effect of DNR unlikely.

At the 2005 assessment, DNR+ survivors showed a decrease of IVSed compared with 1995 (P = .004) and LVPWed showed a tendency to decrease compared with 1995 (P = .08), although most values as such were still within the normal range. Lipshultz et al[2] found a statistically significant change in LVPWed over time and found no dose-related differences. Furthermore, Sörensen et al[5] found a significantly decreased wall thickness in Wilms' tumour survivors at mean 11.1 years since treatment, however these survivors received a much higher dose of anthracyclines (mean, 301 mg/m^2) and the decreased wall thickness was found in combination with a decreased SF. On the other hand, in the same study cardiac function was also studied in ALL-survivors treated with a lower dose of anthracyclines (mean, 180 mg/m^2) and in this group they found no decrease in wall thickness and SF at mean 10.3 years since treatment. In addition, others showed no statistically difference in LVPWed between patients treated with median 240 mg/m^2 anthracyclines and healthy controls, however their median follow-up was only 6.3 years, while our median follow-up was 22 years[3]. We are not aware of studies that noticed a decreased IVSed in childhood cancer survivors treated with anthracyclines. It can be hypothesized that a decreased IVSed and LVPWed might be considered as precursors of future cardiac dysfunction. However, the finding of a normal HRV in the low-dose DNR+ survivors makes this less likely. HRV, reflecting autonomic function, has been described as a sensitive marker of (early) subclinical cardiotoxicity[15]. A previous study in long-term cancer survivors showed progressive deterioration of HRV in survivors treated with medium to high dosages of anthracyclines more than 20 years post-treatment, together with systolic and diastolic dysfunction[12]. Normal HRV results might underline the finding that no cardiac damage has occurred. In order to gain insight in the prognostic significance of echocardiography parameters (such as IVSed and LVPWed) and HRV, continuous follow-up is warranted in these survivors.

Limitations

The echocardiography parameters we used in our study were not quite the same as those used by other authors. Mostly, the parameters of systolic and diastolic left ventricle function used in the several cardiac studies performed in childhood cancer survivors are readily comparable. In paediatric cardiology, SF is commonly used as a primary indicator of systolic function[2,3,5,13]. For a reliable comparison, we also used SF to indicate systolic function. Additionally, WMSI was used as a more sophisticated method to assess systolic function. A difference between our study and those of Lipshultz et al[2] and Nysom et al[13] is the use of z scores to describe the cardiac parameters. Their studies (mainly) concerned children. Z scores are commonly used in paediatric cardiology to adjust for changes in growth, but are less commonly used in adult cardiology. In our current study we did not

use *z* scores as the age of all participants was ≥18 years. Diastolic function in anthracycline-treated childhood cancer survivors was studied by Elbl et al[3], who used a combination of parameters to indicate diastolic function, e.g. E/A ratio, deceleration time, and isovolemetric relaxation time. We used a slightly different combination of parameters to indicate diastolic function, e.g. E/A ratio and TVI Et. TVI Et is an interesting new parameter for assessment of diastolic function and it is more sensitive as it is independent of left ventricular filling. The use of not exactly the same methods might impede comparison of our results with those of others. However, the use of new, more sophisticated and sensitive parameters in assessment of systolic and diastolic function (e.g. WMSI and TVI Et) decreases the chance of underestimation of cardiac dysfunction in low-dose anthracycline-treated childhood cancer survivors. Another limitation of our study is the small cohort of survivors. This causes less power in the statistical analysis. On the other hand, the value of our study is its very long-term follow-up with two subsequent echocardiography evaluations in survivors treated with a low dose of anthracyclines.

In conclusion, no clinical relevant echocardiographic abnormalities were found in childhood ALL-survivors treated with a cumulative dose of 100 mg/m^2 DNR. The prognostic significance of the changes in some cardiac parameters, like IVSed, LVPWed and E/A ratio, is still largely unknown and has to be elaborated. Therefore, we need to continue sequential follow-up assessments, also in survivors treated with lower doses of anthracyclines.

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CHAPTER 6

Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer

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ABSTRACT

Purposes. To assess the prevalence of systolic and diastolic dysfunction after potentially cardiovascular-toxic childhood cancer treatment and the treatment-related risk factors of systolic and diastolic dysfunction in childhood cancer survivors (CCS).

Patients and methods. A cross-sectional single center cohort study in 277 adult CCS (median age at diagnosis 9 (range 0-20) years and current age 28 (18-48) years) treated between 1976-1999 with anthracyclines, platinum and/or radiotherapy (RT). Between 2004-2007 cardiac assessment was performed, including echocardiography, baroreflex sensitivity measurement and assessment of plasma N-terminal pro-brain natriuretic peptide. Results of the CCS were compared with those of 130 sibling controls (median age 26 (range 18-51) years). The main outcome measures were systolic dysfunction (wall motion score index > 1.00) and diastolic dysfunction (Tissue Velocity Imaging of early diastole (TVI Et) mean < 8.00 cm/sec).

Results. At median 18 (range 5-31) years post-treatment, we found a higher prevalence of systolic dysfunction (15% *vs.* 2%) and diastolic dysfunction (12% *vs.* 1%) in the CCS compared with the controls. Seventy-one percent of the CCS with diastolic dysfunction had no systolic dysfunction. A higher cumulative anthracycline dose was associated with systolic and diastolic dysfunction, while chest-RT was only associated with diastolic dysfunction.

Conclusions. After potentially cardiovascular-toxic anticancer treatment 23% of the CCS had systolic and/or diastolic dysfunction. Anthracycline dose and chest-RT were risk factors for diastolic dysfunction. Diastolic dysfunction may be a prognostic factor for clinical heart failure development after childhood cancer treatment and needs to be explored as an intervention target.

INTRODUCTION

Cardiotoxicity is one of the most devastating late effects in childhood cancer survivors (CCS) [1]. CCS are fifteen times as likely to develop clinical heart failure compared with sibling controls [2]. Thus far, cardiac morbidity in CCS is mainly characterized by systolic dysfunction [3,4]. For diastolic cardiac dysfunction only a limited number of small studies is available [5-9]. In the general population, both systolic and diastolic dysfunction are strong predictors for clinical heart failure [10-13].

The increased risk of systolic dysfunction in association with previous anthracycline treatment is well known [3,4,14,15], especially after a higher cumulative dose [3,4]. It has been suggested that anthracycline treatment may also be associated with diastolic dysfunction [8,9]. The influence of radiotherapy (RT) of the chest on the occurrence of cardiac damage is not clear and the data are conflicting [15,16]. Some studies showed that chest-RT was associated with diastolic dysfunction with preservation of systolic function [17], while others have found both systolic and diastolic dysfunction in chest-RT-treated survivors [18] or no association at all with systolic dysfunction [4].

Most studies on diastolic dysfunction in CCS used load-dependent echocardiography parameters [5,7-9,18,19]. However, diastolic function is currently considered to be best detected by load-independent parameters [20]. Thus far, load-independent parameters have only been used in a small study of twenty survivors of adult cancer. In that study, diastolic function was found to be progressively impaired at mean 3.5 years post-treatment compared with baseline measurements at diagnosis [21].

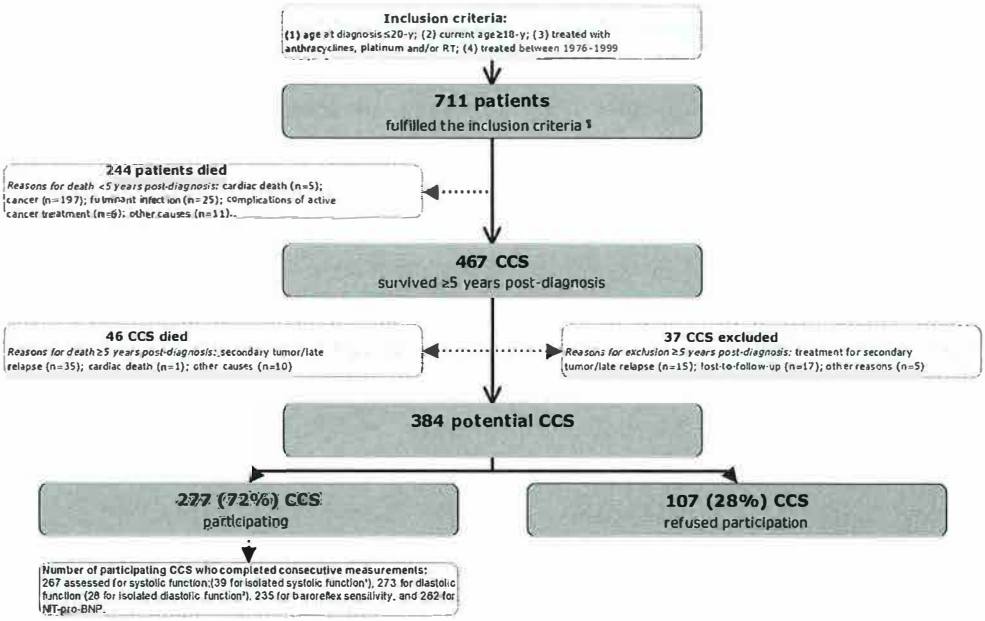
In the current study we assessed the prevalence of clinical and subclinical systolic and diastolic dysfunction in a large cohort of adult CCS five or more years after completing potentially cardiovascular-toxic anticancer treatment and we compared these results with those of sibling controls. Additionally, the association between systolic and diastolic dysfunction with previous childhood cancer treatment was assessed.

PATIENTS AND METHODS

Study design & participant's eligibility and recruitment

The eligibility criteria were (a) childhood cancer diagnosis between 1976 and 1999, (b) potentially cardiovascular-toxic cancer treatment (anthracyclines, platinum and/or head-/neck-/spinal-/trunk-RT), (c) age at diagnosis ≤ 20 years, (d) current age ≥ 18 years and (e) no pre-existent cardiovascular disease and/or Down syndrome. These criteria were fulfilled by 711 patients of whom 244 died within five years post-diagnosis (Figure 1). Eighty-three patients were excluded for various reasons (Figure 1). Two hundred seventy-

Figure 1. Enrollment of long-term CCS in the cross-sectional cardiac study.



Note: CCS, childhood cancer survivors; RT, radiotherapy; § Exclusion criteria: patients with Down syndrome (n = 7) or existent cardiac failure before diagnosis (n = 0); ¹, systolic dysfunction without diastolic dysfunction; ², diastolic dysfunction without systolic dysfunction.

seven of the remaining 384 (72%) CCS agreed to participate in the study. No differences in age at diagnosis, sex, duration of cancer treatment and type of cancer treatment were found between the 277 participating and the 107 non-participating CCS. Twenty-seven of the 277 participating CCS (10%) in this study had received treatment for a relapse. At the time of the cardiac assessment, all 277 CCS were ≥ 5 years after completion of cancer treatment. A control group (comparable by age and sex) was recruited from the siblings of the participants (n = 130).

The study protocol was approved by the Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all participants. All assessments were performed between August 2004 and April 2007.

Methods

CCS and controls underwent assessment of medical history, physical examination, blood sampling, echocardiography and baroreflex sensitivity (BRS).

Medical history was assessed by standardized interview. Details of previous cancer

treatment and medication were retrieved from medical records. Blood pressure was measured twice on both arms in supine position in a quiet room after a minimal rest period of ten minutes. The criteria for hypertension were systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or treatment with antihypertensive drugs. Eight CCS received cardioactive medication (ACE-inhibitor, ß-blocker or diuretic) for systolic heart failure (n = 7) or tubular dysfunction (n = 1) and were excluded from the analysis of the prevalence of hypertension. Body mass index (BMI; weight (kg)/(height)^2 (m^2)) was used as an indicator of body composition.

After an overnight fast, blood was drawn and analyzed for serum lipid levels (total, LDL- and HDL-cholesterol and triglycerides), troponin and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Plasma troponin measurement was by troponin I (normal < 0.04 µg/L) until March 2006 and by troponin T (normal < 0.01 µg/L) afterwards, according to laboratory routine. NT-pro-BNP was measured in heparin plasma stored at -80°C using an immuno-assay (Elecsys 2010; Roche Diagnostics, Lewes, UK; normal value ≤ 125 ng/L).

Echocardiography was performed by a single skilled technician (masked to the treatment versus control group) on a General Electric VIVID 7 system with a 2.5mHz probe and consisted of two-dimensional echocardiography, color flow mapping and 2D-guided M-mode, blood pool and tissue velocity imaging [22]. Dimensions (by example the left ventricular [LV] end-diastolic dimension [LVEDD] and LV end-systolic dimension [LVESD]) were measured as previously described in detail [8] and were corrected for body surface area. Systolic function was determined by shortening fraction (SF; LVEDD-LVESD/LVEDD x 100%) and wall motion score index (WMSI). A SF < 29% was considered abnormal. For the regional analysis of LV systolic function, the LV wall was divided into sixteen segments. Each segment was visually scored between 1 and 4 (1=normokinesia; 2=hypokinesia; 3=akinesia; 4=dyskinesia). WMSI was derived by adding the scores assigned to each segment and dividing the total score by the number of analyzed segments. For the determination of WMSI as an overall measure of systolic function, assessment of ≥12 segments of the LV wall was required. A WMSI >1.00 indicated systolic dysfunction. "Systolic failure" was considered to be present if the WMSI was ≥1.50 and/or if medication for systolic heart failure was used. Diastolic function measurements included mitral valve inflow velocities in early (E) and late (A) diastole and diastolic tissue velocity at the mitral valve annulus (Tissue Velocity Imaging of early diastole (TVI Et)). TVI Et was measured at four segments, that is, septal, lateral, anterior and posterior, and the mean value of these segments was calculated. Diastolic dysfunction was defined as TVI Et mean < 8.0 cm/sec. Additional parameters for diastolic function were E/A-ratio (< 1.00 is considered abnormal) and E/TVI Et (E/E')-ratio [23].

Cardiac autonomic function was assessed using BRS calculated from Finapres blood pressure and heart rate recordings as previously described in detail [24]. BRS (ms/mmHg) was determined by the transfer function technique using the CARSPAN software program and values were given as natural logarithms [25,26].

Definition of cancer treatment groups

The chemotherapy subgroups were defined as (1) any chemotherapy, (2) combination chemotherapy including anthracyclines (Doxorubicin, Daunorubicin) and (3) combination chemotherapy including platinum (Cisplatin, Carboplatin). Based on results of other studies [8,27], we subdivided the cumulative anthracycline dose into anthracycline dose ≤ 225 and > 225 mg/m^2. The RT subgroups were defined as (1) any type of RT and (2) chest-RT (RT of mediastinum, mantle field, total lung, spine or total body-RT (TBI)). Retrospective individual dosimetry on cardiac structures was not available. Cardiac radiation dose was considered to be low in the CCS who received spinal-RT (≤ 45 Gy spinal-RT, estimated RT dose on the heart < 25 Gy) [28] or TBI (≤ 12 Gy TBI, estimated RT dose on the heart < 20 Gy) [29]. Therefore, we defined an additional subgroup for mediastinal-RT (RT to the mediastinum, mantle field or total lung).

Data analyses and statistics

Statistical analyses were performed in SPSS Inc. version 14. Parameters with a non-Gaussian distribution were analyzed by non-parametric tests and parameters with a Gaussian distribution by parametric statistical tests. Two-sided *P*-values <.05 were considered significant.

Multiple logistic and linear regression analyses were used to study the influence of the cancer treatment on the primary outcome measurements (systolic dysfunction, indicated by WMSI > 1.00, and diastolic dysfunction, indicated by TVI Et mean < 8.00 cm/sec) and on the secondary outcomes (abnormal NT-pro-BNP [> 125 ng/L] and BRS). All regression models were adjusted for possible confounders, that is, age at diagnosis, sex, current age, follow-up period post-treatment, hypertension, BMI and use of potentially interfering medication (ACE-inhibitor, diuretic, ß-blocker or GH-replacement therapy).

RESULTS

Study population

Two hundred seventy-seven CCS underwent cardiac assessment at the median of 18 years post-treatment (range 5-31). The treatment characteristics of the participants are summarized in Table 1. Basic characteristics and cardiovascular risk factors are summarized in Table 2. Distribution of age and sex was comparable between CCS and controls (n = 130).

Table 1. Treatment-related Characteristics of the Participating 277 Survivors

	Survivors (n = 277)
Age at diagnosis – years *	8.8 (0.0 – 20.1)
Follow-up post-treatment – years *	18.2 (5.4 – 30.8)
Cancer diagnosis, No (%)	
Leukemia	113 (41)
Malignant lymphoma	56 (20)
Sarcoma	48 (17)
Brain tumor	32 (12)
Blastoma	23 (8)
Germ cell tumor	5 (2)
Chemotherapy, No (%)	
Any chemotherapy	249 (90)
Anthracyclines	199 (72)
Anthracycline dose >225 mg/m^2	90 (32)
Platin	22 (8)
Radiation therapy, No (%)	
Any radiation therapy	174 (63)
Chest-RT [1]	69 (25)
Mediastinal-RT [2]	33 (12)
TBI	17 (6)
Spinal-RT	19 (7)
Radiation dose of mediastinal-RT [2] ≥25 Gy	18 (6)
Combination of treatment modalities, No (%)	
Chest-RT & anthracyclines	45 (16)

Note. No, number; *, median (range); RT, radiotherapy; [1], defined as RT of total lung, mediastinum, mantle field, spine or total body irradiation (TBI); [2], defined as RT to the mediastinum, mantle field or total lung.

Fifteen of the 277 (5%) CCS and none of the controls suffered from systolic failure. Two of them were classified as New York Heart Association Class 2, the remaining 13 as Class 1. Of the 15 CCS with systolic failure, 10 were already on cardioactive medication at the time of the study and five were newly diagnosed. Five of the 15 CCS with systolic failure also had diastolic dysfunction.

Cardiac parameters in CCS and controls (Table 3)

Overall, 23% of the CCS versus 2% of the controls ($P < .001$) had systolic and/or diastolic dysfunction. The prevalence of systolic dysfunction was 15% versus 2% of the controls ($P < .001$). Median SF was lower in the CCS ($P = .012$). Diastolic dysfunction was found in 12% of the CCS versus 1% of the controls ($P < .001$). Seventy-one percent of the CCS with diastolic dysfunction had isolated diastolic dysfunction (i.e., no systolic dysfunction). TVI Et mean and E/A-ratio were lower in the CCS compared with the controls, while E/E'was higher. No difference in frequency of abnormal E/A-ratio was found ($P = .084$). Seventeen of the 29

Table 2. General Characteristics and Cardiovascular Risk Factors

	Survivors (n = 277)	Controls (n = 130)	*P* value
Characteristics			
Sex, No (%)			.40
Male	155 (56)	67 (52)	
Female	122 (44)	63 (48)	
Age at cardiac evaluation – years *	27.5 (18.1-48.2)	25.9 (18.0-51.1)	.33
NYHA classification DC, No (%)			.11 [F]
Class 1	263/274 (96)	129/130 (99)	
Class 2	11/274 (4)	1/130 (1)	
Use of cardiac medication, No (%)	17/275 (6)	0/130 (0)	.004
Use of statins, No (%)	2/275 (1)	0/130 (0)	1.00 [F]
Growth hormone replacement therapy, No (%)	14/275 (5)	0/130 (0)	.006 [F]
Current/ past smoking, No (%)	102/275 (37)	62/130 (48)	.04
Cardiovascular risk factors			
Hypertension [¶], No (%)	38/263 (14)	10/130 (8)	.05
BMI (kg/m^2) *	22.8 (16.4-46.3)	23.7 (17.6-35.0)	.07
Underweight (BMI < 18.5 kg/m^2; No (%))	19/274 (7)	1/130 (1)	.008
Overweight (BMI ≥ 25 kg/m^2; No (%))	91/274 (33)	48/130 (37)	.46
Hypercholesterolemia [¥], No (%)	80/245 (33)	33/123 (27)	.25

Note:*, median (range); No, number; NYHA, New York Heart Association; NYHA Class 1, indicated no symptoms and no limitation in ordinary physical activity; NYHA Class 2, indicated mild symptoms and slight limitation during ordinary activity and comfortable at rest; DC, cardiac failure; BMI, body mass index; [F], *P* values based on Fisher's exact test. [¶], hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive medication (excluding 8 survivors with cardiac treatment because of a cardiomyopathy (n=7) or tubular dysfunction (n=1) and without hypertension) [¥], hypercholesterolemia: fasting LDL-cholesterol ≥ 3.4 mmol/L and/ or use of cholesterol lowering medication (statins)

(59%) CCS with diastolic dysfunction had hypertension versus 19/231 (8%) CCS without diastolic dysfunction (*P* < .001).

NT-pro-BNP was significantly higher and more often elevated in the CCS compared with the controls. NT-pro-BNP was abnormal in 12/38 (32%) CCS with systolic dysfunction and in 4/30 (13%) CCS with diastolic dysfunction. Eighteen of the 31 (58%) CCS with an abnormal NT-pro-BNP had no systolic or diastolic dysfunction. On the other hand, 48/61 (79%) CCS with systolic and/or diastolic dysfunction had a normal NT-pro-BNP. Troponin was abnormal in 3/268 (1%) CCS versus none of the controls (*P* = .55). None of the CCS with systolic and/or diastolic dysfunction had an abnormal troponin. The mean BRS was significantly lower in the CCS compared with the controls (P = .01), indicating autonomic dysfunction in the CCS. BRS was associated with diastolic dysfunction (P = .001), not with systolic dysfunction (P = .29).

Table 3. Cardiac Parameters between Survivors and Controls

	Survivors (n = 277)	Controls (n = 130)	*P* value
Echocardiography – systolic function			
SF (%) ¥	31.6 (6.2)	33.2 (5.3)	.01
Systolic dysfunction: WMSI > 1.00, No (%)	39/267 (14.6)	2/128 (1.6)	<.001
Isolated systolic dysfunction [1]	31/39 (79)	2/2 (100)	1.00[F]
Echocardiography – diastolic function			
E/A-ratio ¥	1.63 (0.50)	1.74 (0.41)	.02
E/A-ratio < 1.00, No (%)	14/273 (5.1)	2/130 (1.5)	.08
TVI Et mean (cm/sec) ¥	10.6 (2.2)	12.4 (1.6)	<.001
E/E'	8.6 (5.1 – 30.0)	7.7 (4.7 – 12.5)	<.001
Diastolic dysfunction: TVI Et mean < 8.00 cm/sec, No (%)	32/273 (11.7)	1/129 (0.8)	<.001
Isolated diastolic dysfunction [2]	20/28 ° (71)	1/1(100)	1.00[F]
Echocardiography			
Systolic and/or diastolic dysfunction [3],No (%)	63/271 (23)	3/127 (2)	<.001
Cardiac autonomic function			
Natural log mean BRS (ln(ms/mmHg)) ¥	2.4 (0.6) (range 0.6 – 4.1)	2.6 (0.6) (range 0.9 – 5.3)	.01
Biochemical cardiac assessment			
NT-pro-BNP (ng/L) *	47 (11 – 4758)	34 (11 – 257)	<.001
NT-pro-BNP > 125 ng/L, No (%)	32/262 (12.2)	4/127 (3.1)	.004
Abnormal Troponin, No (%)	3/268 (1.1)	0/130 (0)	.55[F]
Echocardiography – cardiac dimensions (in mm; BSA-corrected)			
BSA *	1.85 (1.28 – 2.64)	1.92 (1.55 – 2.42)	.001
IVSed ¥	4.3 (0.5)	4.3 (0.6)	.85
LVPWed ¥	4.3 (0.6)	4.2 (0.5)	.13
LVEDD ¥	25.3 (2.4)	25.1 (2.0)	.41
LVESD ¥	17.3 (2.3)	16.8 (2.1)	.03
LA parasternal ¥	17.5 (1.9)	17.5 (1.7)	.98
LA length ¥	28.2 (2.8)	28.0 (2.6)	.37
LA transverse ¥	21.0 (2.8)	21.0 (2.4)	.92
Echocardiography – other parameters			
Valve dysfunctions, No (%)	63/275 (22.9)	29/130 (22.3)	.89

Note. ¥, mean (SD); *, median (minimum-maximum); No (%), number (%); WMSI, wall motion score index; SF, shortening fraction; E/A-ratio, ratio of mitral valve inflow velocities in Early (E) and late (A) diastole; TVI Et, Tissue Velocity Imaging of early diastole; E/E', ratio E velocity/ TVI Et mean; [1], systolic dysfunction (WMSI >1.00) with normal diastolic function (TVI Et mean ≥8.00 cm/sec); [2], diastolic dysfunction (TVI Et mean <8.00 cm/sec) with normal systolic function; [3], systolic dysfunction (WMSI >1.00) and/or diastolic dysfunction (TVI Et mean <8.00 cm/sec); BRS, baroreflex sensitivity; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; BSA, body surface area (m^2), calculated by the formula $0.007184 \times (\text{height})^{0.725} \times (\text{weight})^{0.425}$; IVSed, interventricular septal thickness end-diastolic; LVPWed, left ventricular posterior wall thickness end-diastolic; LVEDD, left ventricular end-diastolic dimension measured in 2D; LVESD, left ventricular end-systolic dimension measured in 2D; LA, left atrium; [F], *P* values based on Fisher's exact test; °, 4 survivors with diastolic dysfunction had no available measurement of systolic function.

Table 4. Multiple Logistic Regression Analysis with Systolic and Diastolic Dysfunction as Dependent Variables

Dependent variables:	**WMSI > 1.00**		**TVI Et mean < 8.00 cm/sec**	
Independent variables ¶:	OR	95% CI	OR	95% CI
Any chemotherapy *(n = 249)*	1.10	0.25 – 4.94	3.24	0.33 – 31.94
Anthracyclines *(n = 199)*	1.59	0.58 – 4.40	1.46	0.43 – 4.99
Cumulative dose of anthracyclines (by 100mg/m^2)	**1.42**	**1.08 – 1.85**	1.19	0.87 – 1.62
Dose anthracyclines > 225 mg/m^2 *(n = 90)*	**2.73**	**1.23 – 6.05**	**3.11**	**1.03 – 9.40**
Platin *(n = 22)*	0.67	0.16 – 2.72	2.29	0.33 – 15.95
Any RT *(n = 174)*	0.82	0.37 – 1.81	0.84	0.27 – 2.61
Chest-RT [1] *(n = 69)*	1.05	0.45 – 2.45	**4.27**	**1.42 – 12.87**
Chest-RT [1] by localization:				
Mediastinal-RT [2] *(n = 33)*	1.40	0.45 – 4.29	**10.33**	**2.97 – 51.14**
TBI *(n = 17)*	0.78	0.17 – 3.50	1.62	0.10 – 25.14
Spinal-RT *(n = 19)*	0.79	0.12 – 5.25	0.74	0.08 – 6.92
Dose of mediastinal-RT [2] ≥ 25 Gy *(n = 18)*	2.58	0.71 – 9.44	**26.63**	**4.51 – 157.25**
Combination of chest-RT by localization & cumulative dose of anthracyclines >225 mg/m^2 in 1 model:				
Chest-RT [1] by localization				
Mediastinal-RT [2]	1.85	0.58 – 5.88	**16.37**	**3.58 – 74.80**
TBI	0.88	0.19 – 4.11	2.87	0.17 – 47.29
Spinal-RT	0.97	0.14 – 6.76	1.52	0.14 – 16.23
Cumulative dose of anthracyclines > 225 mg/m^2	**2.93**	**1.29 – 6.66**	**4.52**	**1.23 – 16.60**

Note. ¶, multivariate regression analysis with "fixed" confounding variables age at diagnosis, follow-up period post-treatment, current age, sex, hypertension, potentially interfering medication (ACE-inhibitor, ß-blocker, diuretic or growth hormone replacement therapy) and body mass index; CI, confidence interval; RT, radiotherapy; TBI, total body irradiation; [1] chest-RT, including RT to the mediastinum/mantle field/total lung, TBI or spinal-RT; [2] mediastinal-RT, defined as RT to the mediastinum/mantle field or total lung; WMSI, wall motion score index; TVI Et, Tissue Velocity Imaging of early diastole; n, number. **Bold typed**, significantly associated cancer treatment modality.

Cancer treatment-related factors in the development of cardiac dysfunction

By multiple logistic regression analysis it was shown that none of the possible confounders was associated with systolic dysfunction, except for cardiac medication (as part of the definition of systolic failure; odds ratio (OR) 19.6; 95% confidence interval (CI) 3.5-108.9) and GH-replacement therapy (OR 5.2; 95% CI 1.4-20.0). Age (OR 1.3; 95% CI 1.2-1.6), female sex (OR 0.3; 95% CI 0.1-0.97), hypertension (OR 8.4; 95% CI 2.9-24.1) and BMI (OR 1.1; 95% CI 1.0–1.2) were associated with diastolic dysfunction.

Entering the treatment variables in the regression model (Table 4) showed that a higher cumulative anthracycline dose was associated with a higher risk of systolic dysfunction (OR 1.4; 95% CI 1.1-1.9). Chest-RT was not associated with systolic dysfunction. Diastolic

dysfunction was associated with cumulative anthracycline dose > 225 mg/m^2 (OR 3.1; 1.0-9.4) and with chest-RT (OR 4.3; 95% CI 1.4-12.9), especially mediastinal-RT. Finally, cumulative anthracycline dose (OR 1.6; 95% CI 1.2-2.1) and chest-RT specified by mediastinal-RT (OR 3.4; 95% CI 1.1-10.0) were significantly associated with an elevated NT-pro-BNP. None of the treatment factors was associated with BRS (data not shown).

DISCUSSION

In this study we demonstrate a significantly higher prevalence of systolic and diastolic dysfunction in a large cohort of adult survivors of childhood cancer compared with sibling controls. After a median follow-up of 18 years post-treatment, 15% of the CCS had systolic dysfunction compared with 2% of the sibling controls. The prevalence of diastolic dysfunction was also higher in the CCS (12% versus 1%). Most CCS with diastolic dysfunction had no systolic dysfunction (71%). These results are noteworthy, since in the general population not only systolic dysfunction, but also diastolic dysfunction predicts clinical heart failure [10,11,12,13] and sudden cardiac death [11,13].

Cardiac mortality is reported to be about six-fold higher in CCS compared with controls or background population [30,31], while data on cardiac morbidity show variable results. Thus far, cardiac dysfunction has been mainly characterized by parameters of systolic function [3,4,32]. Diastolic function is not well established in CCS and has been described in only a few studies [5-9]. The major drawbacks of these studies are their limited size and the use of load-dependent echocardiography parameters, such as E/A-ratio, that cause conflicting results. Load-dependent diastolic parameters have the disadvantage that differences in LV filling may interfere with correct interpretation [20]. TVI Et, being independent of LV filling, is currently considered the most reliable technique for the assessment of diastolic dysfunction [20]. In our data, we found no difference in prevalence of an abnormal E/A-ratio between CCS and the controls, whereas TVI was more frequently abnormal in the CCS. In survivors of adult cancer, TVI was already used and showed progressive impairment several years after anthracycline treatment when compared with baseline at cancer diagnosis [21]. To the best of our knowledge, the current study is the first one with a reliable estimation of diastolic dysfunction by TVI Et in CCS.

A higher cumulative anthracycline dose was identified as the only significant treatment-related risk factor in the development of systolic dysfunction. We did not find a significant association of previous chest-RT with systolic dysfunction. Recently, Hudson et al assessed systolic function by the load-dependent parameter SF and found that CCS treated with a cumulative anthracycline dose ≥ 270 mg/m^2 had the greatest risk of a decreased SF, while whole heart-RT was not associated with a decreased SF [4]. Other studies on the effect of

cardiac radiation showed conflicting results. Poutanen et al showed that CCS treated with RT of the cardiac region had a lower ejection fraction indicating systolic dysfunction [18], while others found no association between heart-RT and systolic dysfunction [33]. At the time the patients in our study group received RT, the data were not stored, precluding accurate retrospective estimation of the radiation dose to the heart. Therefore, we subdivided the CCS who received chest-RT into subgroups based on an estimation of the radiation dose to the heart, that is, those with mediastinal-RT, those with TBI and those with spinal-RT. The subgroup with the radiation dose presumed highest to the heart, that is, mediastinal-RT, had a non-significant OR of 1.4 (95% CI 0.5-4.3) for systolic dysfunction (Table 4). On the other hand, in participants with diastolic dysfunction both cumulative anthracycline dose > 225 mg/m^2 and chest-RT (in particular mediastinal-RT) were identified as treatment-related risk factors. Previous studies using load-dependent variables suggested that diastolic dysfunction was associated with anthracyclines [6-8] and chest-RT [16,33]. The current study is the first on the load-independent TVI Et measurement for assessment of diastolic function in a large cohort of CCS with a prolonged follow-up post-treatment. Although there was a significant association between hypertension and diastolic dysfunction, more than 40% of the CCS with diastolic dysfunction had no hypertension, thus suggesting additional mechanisms in the etiology of diastolic dysfunction in CCS.

In our study, plasma NT-pro-BNP and BRS were evaluated as additional parameters in cardiac risk assessment. NT-pro-BNP was higher in CCS compared with the controls and a higher cumulative anthracycline dose as well as mediastinal-RT were associated with an elevated NT-pro-BNP. However, there was no relation between the echocardiography findings and an abnormal NT-pro-BNP. Therefore, in this study NT-pro-BNP was not contributory for the detection of cardiac dysfunction. BRS was lower in CCS, suggesting autonomic cardiac dysfunction. However, none of the treatment-factors in this study was found to be associated with BRS. In a previous study of high-dose anthracycline-treated bone tumor survivors who had systolic and diastolic dysfunction, we also observed autonomic dysfunction [8]. Low BRS is a predictor of all-cause mortality and sudden death in various patient groups [34]. In CCS, autonomic dysfunction may be predictive for cardiac morbidity.

The association of diastolic dysfunction with advanced age has been established in the general population [35,12]. One possible underlying cause in the development of diastolic dysfunction is increased vascular and ventricular stiffness, which is an integral manifestation of aging [20]. The finding of an increased prevalence of diastolic dysfunction in young adult CCS at a median age of 28 years suggests precocious cardiovascular aging. Recently, Maccormick et al. elaborated the theoretical mechanisms of aging and the way

in which chemotherapy could possibly accelerate these mechanisms [36]. One of these aging theories is based on the accumulation of free-radical damage. Anthracycline metabolism generates free-radical intermediates that can damage cardiac tissue [36]. Radiation has been described in association with atherosclerosis as an integral component of aging [37,38]. The exact mechanism needs to be elucidated, but RT-induced endothelial injury has been suggested as an initiator in the development of atherosclerosis [37,38]. Further research is warranted to explore the hypothesis of accelerated aging in CCS and its devastating effect on the heart.

Treatment for asymptomatic systolic dysfunction has been well established, but treatment for asymptomatic diastolic dysfunction has yet to be evaluated in clinical trails [13]. Thus far, identification and treatment of the underlying cause(s) of diastolic dysfunction (e,g. hypertension, overweight) remains the current approach to subclinical diastolic dysfunction.

The strengths of our study lie in the large sample size, the extended follow-up, the large cohort of sibling controls and the sophisticated echocardiography. One limitation is the heterogeneity of the cohort. To overcome this, we used logistic regression analyses for the adjustment of possibly confounding variables.

We conclude that CCS who have been treated with potentially cardiovascular-toxic treatment had a markedly increased prevalence of systolic as well as diastolic dysfunction. A higher anthracycline dose was associated with both systolic and diastolic dysfunction, whereas chest-RT was only associated with diastolic dysfunction. Diastolic dysfunction plays a much larger role in long-term CCS than expected up until now and may be of prognostic significance. The course of this diastolic dysfunction over time should be prospectively investigated. Associated risk factors, such as hypertension and overweight, require further exploration as potential intervention targets.

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CHAPTER 7

Vascular damage in long-term childhood cancer survivors

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Submited

ABSTRACT

Purpose. To evaluate (1) vascular damage in long-term childhood cancer survivors (CCS) and sibling controls; (2) the association between vascular damage and cancer treatment; (3) the association between vascular damage and cardiovascular risk factors.

Patients and methods. We included 277 adult CCS (median age at diagnosis 9 (range: 0-20) years treated between 1976-1999 with anthracyclines, platin and/or radiotherapy (RT). Vascular assessment consisted of determination of the carotid and femoral intima-media thickness (IMT) and flow-mediated vasodilatation of the brachial artery by ultrasound and determination of endothelial and inflammatory marker proteins (including tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-I)) and cardiovascular risk factors. Results of the CCS were compared with those of 130 age- and sex-matched siblings (median age 26 (18-51) years)

Results. At median 18 (5-31) years post-treatment and median age of 28 (18-48) years, carotid and femoral IMT were not different between CCS and controls. However, a higher carotid and femoral IMT were found in CCS treated with any RT. In CCS, t-PA and PAI-I were higher compared with controls, indicating endothelial damage. The prevalence of cardiovascular risk factors (i.e. hypertension, hypercholesterolemia, overweight) was higher in CCS with a higher t-PA, PAI-I, carotid and/or femoral IMT.

Conclusion. After potentially cardiovascular-toxic anticancer treatment, CCS treated with RT had a higher carotid as well as femoral IMT. Compared with controls, CCS had more signs of endothelial damage and an unfavorable cardiovascular risk profile. A higher carotid/ femoral IMT and endothelial damage were associated with more cardiovascular risk factors.

INTRODUCTION

Cardiovascular disease is one of the most common late effects in childhood cancer survivors (CCS) [1,2]. The prevalence of clinical cardiovascular disease [2-4] as well as the prevalence of preclinical cardiovascular damage are markedly increased in CCS compared with the background population.

An increased arterial intima media thickness (IMT) is generally considered as an early marker of atherosclerosis and is associated with an increased risk of myocardial infarction and stroke [5]. Carotid artery IMT was higher in small studies of CCS following cranial and/or neck radiotherapy (RT) [6,7]. Endothelial damage is one of the initial steps in the development of cardiovascular disease. Small studies in cancer survivors demonstrated impaired endothelium-dependent vasodilatation after treatment with RT or anthracyclines[8-11]

In survivors of adult cancer, we and others have shown that early signs of vascular damage were frequently accompanied by an unfavorable cardiovascular risk profile [8,12]. Others found an elevated systolic blood pressure, dyslipidemia and a higher carotid bulb IMT in 26 survivors of childhood brain cancer treated with craniospinal RT [6]. An increased prevalence of cardiovascular risk factors was also found in survivors of childhood acute lymphoblastic leukemia, especially when treated with cranial RT [13].

We therefore performed a cross-sectional study on vascular damage and vascular function in a large cohort of adult CCS five or more years after completion of potentially cardiovascular-toxic anticancer treatment. The objectives were to evaluate (1) the parameters of vascular damage (carotid IMT and femoral IMT as primary outcome measures; endothelial- and inflammatory marker proteins as secondary outcome measures) in long-term CCS in comparison with results of controls; (2) the association between the vascular parameters and the previous childhood cancer treatment and (3) the association between the vascular damage and the cardiovascular risk factors.

PATIENTS & METHODS

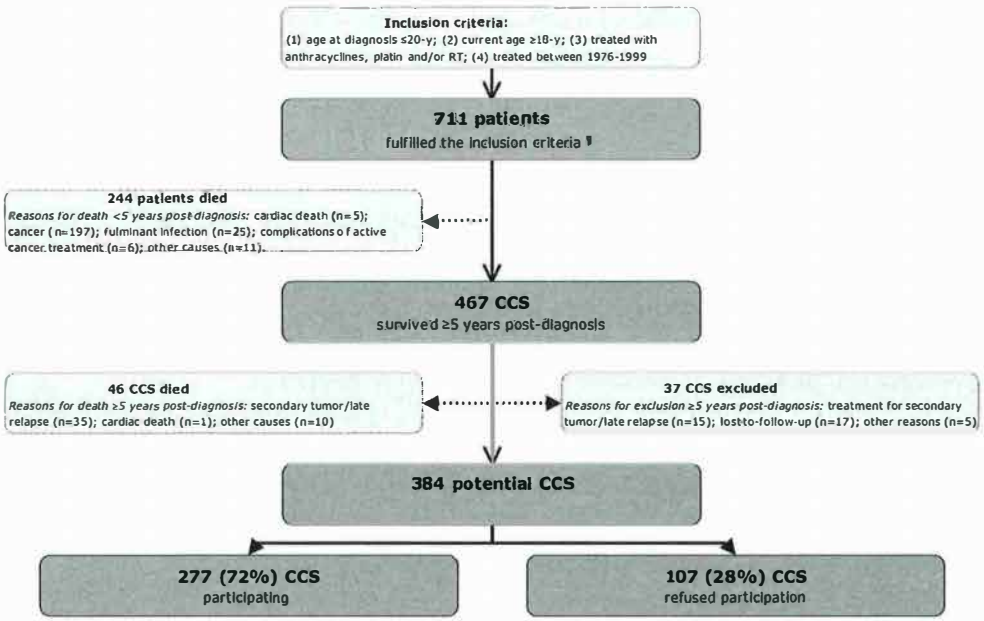
Study design & population

Eligibility criteria were (a) childhood cancer diagnosis between 1976 and 1999; (b) potentially cardiovascular-toxic cancer treatment (anthracyclines, platin and/or head-/neck-/spinal-/trunk-RT); (c) age at diagnosis ≤ 20 years; (d) current age ≥ 18 years; (e) no pre-existent cardiovascular disease and/or Down syndrome. The eligibility criteria were fulfilled by 711 patients of whom 290 died: 244 within 5 years post-diagnosis and 46 thereafter (Fig. 1). Another 37 patients were excluded for other reasons (Fig 1). Of the remaining 384 eligible CCS, 277 (72%) CCS agreed to participate. No differences in age

at diagnosis, sex, duration of cancer treatment and type of cancer treatment were found between those who participated and those who refused. Age- and sex-matched controls were recruited among siblings of the participants (n = 130).

The study protocol was approved by the Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all participants. All assessments were performed between August 2004 and April 2007.

Figure 1. Enrollment of Long-Term Childhood Cancer Survivors in the Cross-Sectional Vascular Study



Note: CCS, childhood cancer survivors; RT, radiotherapy; ¶ Exclusion criteria: patients with Down syndrome (n = 7) or existent cardiac failure before diagnosis (n = 0).

Methods

Information regarding previous cancer treatment, current use of medication and smoking were obtained from the medical records. A physical examination was performed with measurement of blood pressure (twice on both arms in supine position after ≥ 10 minutes rest), height, weight, waist and hip circumference. Criteria for hypertension were systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or treatment with antihypertensive drugs. Eight CCS received cardioactive medication for cardiac failure (n = 7) or tubular dysfunction (n = 1) and were excluded from the analysis of the prevalence of hypertension. Body mass index (BMI) was calculated by the formula weight (kg)/(height)^2 (m^2) and waist-to-hip ratio (W/H-ratio) by dividing waist circumference (cm) by hip

circumference (cm). Both BMI and W/H-ratio were used as indicators of body composition. Underweight was defined as a BMI < 18.5 kg/m^2 and overweight as a BMI ≥ 25 kg/m^2.

Vascular structure was determined by IMT measurements using ultrasound (Acuson Corp.128 XP ultrasound system, Mountain View, CA) with a 7 MHz linear array transducer, as described before [14,15]. The far wall segments of the common carotid artery, carotid bulb and internal carotid were imaged from a lateral transducer position, of the common and the superficial femoral arterial walls from an anterior transducer position. All images were saved and analyzed off-line. The highest IMT value found in a segment was considered to be the maximum IMT and the mean of three measurements in this segment was considered to be its mean IMT. The endpoint was the mean maximal thickness of the far wall IMT of the 6 imaged carotid segments and of the 4 femoral segments. From studies on reproducibility, the error of variation in measurement is calculated as 0.03 mm for the primary endpoint, combined carotid and femoral far wall IMT.

Vascular function was assessed by brachial flow-mediated dilation (FMD), using a wall tracking system consisting of an ultrasound scanning device (Wall Tracking System 2.0, Pie Medical Esaote AU-5 and Wall Tracking System 2.0 software, Pie Medical, Maastricht, the Netherlands) as described earlier [16]. In short, a 7.5 MHz ultrasound probe was placed in a probe-holding device to ensure a stable positioning, approximately 2 cm above the arm using a gel-pad. A pneumatic tourniquet was placed around the forearm, distal to the scanned artery segment, with the arm supported to prevent movement during cuff inflation. The diameter of the brachial artery was measured twice before inducing ischemia and the mean value was indicated as the baseline diameter. The cuff was inflated (250 mmHg) for 4 minutes to induce ischemia. M-mode signals obtained of the brachial artery were stored and analysed off-line. Mean end-diastolic diameter for each recording was used to calculate FMD. FMD was calculated as the maximum percentage increase in diameter of the brachial artery compared with the mean baseline diameter (software: AIM-WTS, Vascular Laboratory, Groningen, the Netherlands). All measurements were performed by a single technician blinded for participants' characteristics. Using this standardized setup, the intra- and inter-observer variability for the assessment of baseline diameter are 1.1% and 3.8%, respectively. The coefficient of variation of the FMD-measurement is 13.9% [17].

Fasting blood samples were analyzed according to routine laboratory procedures for lipid spectrum (plasma total, LDL- and HDL-cholesterol and triglycerides; mmol/L), glucose (plasma; mmol/L), insulin (serum; mU/L), creatinine (plasma; µmol/L) and cystatin C (plasma; mg/L). Hypercholesterolemia was defined as fasting LDL-cholesterol ≥ 3.4 mmol/L and/or use of cholesterol lowering medication. Homocysteine (normal value < 10 µmol/L) was

analyzed using the BNII Nephelometer (Dade Behring, Marburg, Germany). The insulin-to-glucose ratio and the HOMA-index (fasting insulin (mU/L) x fasting glucose (mmol/L)/ 22.5) were calculated as measures of insulin sensitivity. A HOMA-index above 2.0 is known to be associated with an increased risk of stroke and cardiovascular disease[18].

Fibrinogen (citrate plasma; g/L) was measured using the Clauss functional assay and high-sensitivity C-reactive protein (serum; hsCRP; mg/L) by using the BNII Nephelometer. Von Willebrand factor (vWF; %) was measured in citrate plasma by an enzyme-linked immunosorbent assay (ELISA) using polyclonal (conjugated) antibodies from Dako A/S (Glostrup, Denmark). Plasminogen activator inhibitor type I antigen (PAI-1; µg/L) and tissue-type plasminogen activator antigen (t-PA; µg/L) were determined in citrate plasma by ELISA Asserachrom PAI® and Asserachrom tPA® (Roche, Basel, Switzerland).

A 24-h urine sample was analyzed for albumin (mg/L) and creatinine (mmol/L) content. Renal function was assessed in a 24-h urine sample and calculated by the formula: (urinary creatinine x 1000)/ plasma creatinine) x (volume 24-h urine/1440) x (1.73/ body surface area) (mL/min/1.73 m^2). Outcomes of 60 mL/min/1.73 m^2 or lower were defined as renal dysfunction. Urinary albumin-excretion was determined by nephelometry. Albuminuria was defined as a urinary albumin-excretion ≥ 30 mg/24-h. Additionally, the albumin-to-creatinine ratio was calculated in a 24-h urine sample.

The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP APT III)[19]. CCS who received cardioactive medication (n = 8) and participants with non-fasting blood samples (n = 20 CCS; n = 4 controls) were not assessed for metabolic syndrome.

Definition of cancer treatment groups

The chemotherapy-subgroups were defined as: (1) any chemotherapy; (2) combination chemotherapy including anthracyclines (doxorubicin, daunorubicin); (3) combination chemotherapy including platin-derivates (cisplatin, carboplatin). The total cumulative dose of anthracyclines was calculated by adding the doses of doxorubicin and daunorubicin as these derivates were considered as equivalents of each other. The RT-subgroups were defined as: (1) any type of RT; (2) cranial-/craniospinal-RT; (3) irradiation of neck (RT of neck, mantle field and/or spine); (4) chest-RT (RT of mediastinum, mantle field, total lung and/ or spine); (5) abdominal-RT (RT of abdomen, pelvic and/or spine); (6) total body irradiation (TBI). Retrospective individual dosimetry was not available as initial cancer diagnoses were between 1976 and 1999.

Data analyses and statistics

Statistical analyses were performed in SPSS inc. version 14. Parameters with a non-Gaussian distribution were analyzed by non-parametric tests and parameters with a Gaussian distribution by parametric statistical tests. Two-sided *P*-values < .05 were considered significant. We used multiple regression analysis to investigate whether the associations between carotid IMT and age and between femoral IMT and age were different for CCS and controls by including an interaction term.

Multiple linear regression analysis was used to assess the influence of the cancer treatment on the primary outcome measures (i.e. carotid and femoral IMT) and on the secondary outcome measures (i.e. endothelial- and acute phase marker proteins: fibrinogen, vWF, PAI-I, t-PA, ratio PAI-I/t-PA, hsCRP; albumin-excretion and albumin/creatinine-ratio in a 24-h urine sample). In the regression models we adjusted for age at diagnosis, sex and age at the vascular assessment.

Cardiovascular risk factors were compared between CCS with an IMT equal or above the 75th percentile (P^{75}; P^{75} of carotid IMT corresponds with 0.65 mm; P^{75} of femoral IMT corresponds with 0.56 mm) and CCS with an IMT below P^{75} with adjustment for age at diagnosis, sex and age at the vascular assessment in a multiple logistic regression analysis. By the same adjusted regression model, we assessed the association between the cardiovascular risk factors and the dependent variables FMD ≤ P^{25} (≤ 1.47%), PAI-I ≥ P^{75} (≥ 27 ng/L) and t-PA ≥ P^{75} (≥ 6.9 ng/mL), and the association between carotid and femoral IMT and the marker proteins.

RESULTS

Study population and cardiovascular risk factors

Median (range) age of the 277 participating CCS was 27.5 (18.1-48.2) years and of the 130 controls 25.9 (18.0-51.1) years. Treatment-related characteristics of the CCS are summarized in Table 1. At the time of the study, 2 (1%) CCS received cholesterol-lowering medication and 17 (6%) cardioactive medication. None of the controls was on cholesterol-lowering or cardioactive medication.

Results of the cardiovascular risk assessment are summarized in Table 2. Hypertension tended to be more prevalent in CCS (P = .054). The prevalence of hypercholesterolemia was not significantly different between CCS and controls. However, the ratio of total cholesterol/ HDL-cholesterol was higher in CCS. Compared with the controls, CCS had more often renal dysfunction, a higher cystatin C and a higher prevalence of the metabolic syndrome. The prevalence of overweight was comparable between CCS and controls, while the prevalence of underweight was higher in the CCS.

Table 1. Treatment-related Characteristics of the Participating 277 Survivors

	Survivors (n = 277)
Median age at diagnosis (range) – years	8.8 (0.0 – 20.1)
Median follow-up post-treatment (range) – years	18.2 (5.4 – 30.8)
Cancer diagnosis, No (%)	
Leukemia	113 (41)
Malignant lymphoma	56 (20)
Sarcoma	48 (17)
Brain tumor	32 (12)
Blastoma	23 (8)
Germ cell tumor	5 (2)
Chemotherapy, No (%)	
Any chemotherapy	249 (90)
Anthracyclines [1]	199 (72)
Platin [2]	22 (8)
Radiation therapy, No (%)	
Any radiation therapy	174 (63)
Cranial-/craniospinal-irradiation	102 (37)
Irradiation of neck [3]	50 (18)
Chest irradiation [4]	53 (19)
Irradiation of abdomen [5]	51 (18)
Total body irradiation	17 (6)

Note. No, number; [1], doxorubicin and/or daunorubicin; [2], cisplatin and/or carboplatin; [3], radiotherapy of neck, mantle field and/or spine; [4], radiotherapy of mediastinum, mantle field, total lung and/or spine; [5], radiotherapy of abdomen, pelvic and/or spine

Vascular damage in association with childhood cancer treatment

Vascular structure as measured by carotid IMT and femoral IMT, vascular function as measured by FMD (Table 3) and the association between the carotid IMT and age at the vascular assessment did not differ between CCS and controls (B of difference was 0.001; 95% confidence interval (CI) -0.002-0.004; $P = .563$). However, the association between femoral IMT and age is significantly higher in CCS (B of difference was 0.004; 95% CI 0.001-0.008; $P = .015$) indicating a more increased femoral IMT with increasing age in CCS. Carotid distensibility was lower in the CCS compared with the controls. Lower mean pressure pulsations in the CCS compensated the lower carotid distensibility, indicated by a non-significantly different carotid compliance. (Table 3)

By multiple linear regression analysis we assessed the relation between the previous cancer treatment and the carotid IMT, femoral IMT and FMD. The carotid IMT was associated with any RT (B = 0.028; $P = .036$), neck-RT (B = 0.048; $P = .003$), chest-RT (B = 0.060; $P < .001$) and abdominal-RT (B = 0.034; $P = .035$) and femoral IMT with any RT (B = 0.029; $P = .032$) and

Table 2. General Characteristics and Cardiovascular Risk Factors

	CCS (n = 277)	Controls (n = 130)	*P*-value
Age at visit – years *	27.5 (18.1 – 48.2)	25.9 (18.0 – 51.1)	.328
Sex (male/female)	155/122	67/63	.404
Hypertension [1], No (%)	38/263 (14%)	10/130 (8%)	**.054**
Systolic blood pressure (mmHg) * ‡	114 (78 – 171)	115 (98 – 156)	**.046**
Diastolic blood pressure (mmHg) * ‡	79 (54 – 120)	77 (55 – 104)	**.037**
Hypercholesterolemia [2], No (%)	80/245 (33%)	33/123 (27%)	.253
Total cholesterol (mmol/L) * °	4.7 (2.9 – 8.0)	4.5 (2.4 – 7.0)	.337
LDL-cholesterol (mmol/L) * °	2.9 (1.3 – 5.5)	2.7 (1.0 – 5.4)	.166
HDL-cholesterol (mmol/L) * °	1.3 (0.7 – 2.2)	1.4 (0.9 – 2.7)	.074
Triglycerides (mmol/L) * °	1.0 (0.3 – 6.7)	1.0 (0.4 – 3.2)	.893
Ratio total cholesterol/ HDL-cholesterol * °	3.5 (2.0 – 8.9)	3.3 (1.7 – 7.8)	**.037**
Overweight [3], No (%)	91/274 (33%)	48/130 (37%)	.463
Underweight [4], No (%)	19/274 (7%)	1/130 (1%)	**.008**
Body mass index (kg/m^2) *	22.8 (16.4 – 46.3)	23.7 (17.6 – 35.0)	.066
Waist-hip ratio *	0.90 (0.71 – 1.17)	0.89 (0.75 – 1.07)	.103
Waist circumference (cm) *	84 (47 – 144)	84 (68 – 121)	.671
Hip circumference (cm) *	94 (62 – 143)	96 (78 – 119)	**.045**
Current smoking, No (%)	70/276 (25%)	43/130 (33%)	.106
Metabolic syndrome [5], No (%)	23/241 (10%)	4/125 (3%)	**.028**
Renal dysfunction [6], No (%)	23/250 (9%)	4/126 (3%)	**.033**
Renal function (mL/min/1.73 m^2) *	95 (21 – 191)	106 (46 – 205)	**.003**
Creatinine (µmol/L) *	71 (42 – 146)	73 (52 – 109)	.207
Cystatin C (mg/L) *	0.81 (0.55 – 1.70)	0.78 (0.51 – 1.10)	**.022**
HOMA-index > 2.0, No (%)	111/238 (47%)	45/122 (37%)	.077
HOMA-index * °	1.9 (0.2 – 18.0)	1.7 (0.5 – 5.4)	.077
Insulin (mU/L) * °	9.6 (1.0 – 78.0)	8.6 (2.6 – 24.2)	.082
Glucose (mmol/L) * °	4.7 (3.1 – 8.7)	4.6 (3.6 – 7.1)	.260
Insulin/glucose ratio * °	2.1 (0.2 – 15.6)	1.8 (0.5 – 10.8)	.078
Homocysteine > 10 µmol/L, No (%)	121/245 (49%)	59/124 (48%)	.743
Homocysteine (µmol/L) * °	10.0 (4.3 – 75.0)	9.9 (5.1 – 23.4)	.653

Note. No, number; CCS, childhood cancer survivors; *, median (range); ‡, excluding 17 CCS with cardioactive medication because of a cardiomyopathy, tubular dysfunction and/or hypertension; HOMA, Homeostasis Model of Assessment. [1], hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive medication (excluding 8 survivors with no hypertension, but with cardioactive treatment because of a cardiomyopathy (n = 7) or tubular dysfunction (n = 1); [2], hypercholesterolemia was defined as fasting LDL-cholesterol ≥ 3.4 mmol/L and/or use of cholesterol lowering medication; [3], overweight was defined as body mass index (BMI) < 18.5 kg/m^2; [4], underweight was defined as a body mass index (BMI) ≥ 25 kg/m^2; [5], metabolic syndrome was determined by ≥ 3 of the following criteria: abdominal obesity (waist circumference in male > 102 cm and in females > 88 cm), a high triglyceride concentration (≥ 1.69 mmol/L), a low HDL cholesterol concentration (in males < 1.04 mmol/L and in females < 1.29 mmol/L), a high glucose concentration (≥ 6.1 mmol/L), or high blood pressure (≥ 130/85 mmHg and/or use of antihypertensive drugs). Excluding persons with cardioactive medication because of a cardiomyopathy or tubular dysfunction and persons with non-fasting blood samples; [6], renal function was measured in a 24h urine sample and renal dysfunction was indicated as ≤ 60 mL/min/1.73 m^2; °, blood samples were taken after an overnight fast.

neck-RT (B = 0.042; $P = .012$). (Table 4) There was no association between FMD and any of the cancer treatment modalities (data not shown).

Marker proteins in association with childhood cancer treatment

Compared with the controls, the CCS had significantly higher t-PA, PAI-I and urinary albumin/creatinine-ratio, while vWF and fibrinogen were similar (Table 3). The association between cancer treatment and the endothelial and inflammatory marker proteins was analyzed in a multiple linear regression model (data shown only for significant associations). Fibrinogen (B = 0.5; 95% CI 0.2-0.8; $P = .003$), t-PA (B = 0.3; 95% CI 0.1-0.5; $P = .001$), PAI-I (B = 0.7; 95% CI 0.3-1.1; $P < .001$) and PAI-I/t-PA-ratio (B = 0.4; 95% CI 0.1-0.7; $P = .009$) were associated

Table 3. Vascular Structure and Function and Marker Proteins

	CCS (n=277)	Controls (n=130)	*P*-value
Vascular function and structure			
IMT carotid artery (mm) *	0.60 (0.46 – 0.98)	0.60 (0.48 – 0.87)	.577
Carotid IMT ≥ 0.65 mm (≥ P^{75}), No (%)	70/270 (26%)	30/130 (23%)	.538
IMT femoral artery (mm) *	0.52 (0.40 – 1.07)	0.52 (0.39 – 0.71)	.722
Femoral IMT ≥ 0.56 mm (≥ P^{75}), No (%)	70/270 (26%)	30/130 (23%)	.538
Baseline BA diameter (μm) ¶	4346 (715)	4366 (659)	.807
Absolute post-ischemic BA dilatation (μm) ¶	4598 (733)	4649 (732)	.548
FMD (%) *	5.3 (-16.8 – 30.7)	5.3 (-7.5 – 31.5)	.508
FMD ≤ 1.47% (≤ P^{25}), No (%)	60/222 (27%)	23/112 (21%)	.195
Carotid compliance (μm/mmHg) *	11.1 (3.0 – 29.0)	12.1 (3.9 – 30.3)	.096
Carotid distensibility (%) *	8.8 (1.8 – 20.0)	10.1 (4.2 – 25.7)	**< .001**
Mean pressure pulsations (mmHg) ¶	55.2 (11.4)	60.9 (13.3)	**< .001**
Endothelial and inflammatory marker proteins			
Fibrinogen (g/L) *	2.7 (1.4 – 6.0)	2.7 (1.3 – 6.3)	.315
Factor VIII Von Willebrand (%) * ‡	87 (28 – 339)	89 (39 – 482)	.956
T-PA (ng/mL) *	5.3 (1.3 – 15.6)	4.2 (1.0 – 13.7)	**< .001**
T-PA ≥ 6.9 ng/mL (≥ P^{75}), No (%)	77/251 (31%)	17/120 (14%)	**.001**
PAI-I antigen (ng/mL) *	16 (3 – 197)	12 (3 – 116)	**.006**
PAI-I antigen ≥ 27 ng/mL (≥ P^{75}), No (%)	68/251 (27%)	26/120 (22%)	.261
PAI-I / t-PA-ratio *	3.2 (0.9 – 50.8)	3.1 (0.9 – 16.6)	.973
hsCRP (mg/L)*	1.3 (0.1 – 47.8)	1.3 (0.1 – 67.8)	.608
Albumin in 24-h urine (mg/24-h) *	7.5 (0 – 2405)	6.7 (0 – 186)	.154
Albuminuria (≥ 30 mg/24-h), No (%)	23/244 (9%)	10/123 (8%)	.682
Albumin/creatinine-ratio (mg/mmol; in 24-h urine) *	0.7 (0 – 167)	0.6 (0 – 18)	**.003**

Note. No, number; CCS, childhood cancer survivors; *, median (range); ¶, mean (SD); F, *P* values based on Fisher's exact test; IMT, intima media thickness; BA, brachial artery; FMD, flow-mediated vasodilatation; ‡, comparison of Factor VIII Von Willebrand between male CCS and male controls and between female CCS and female controls (with/without oral conceptiva) showed no significant differences; t-PA, tissue-type plasminogen activator; PAI-I, plasminogen activator inhibitor type 1; hsCRP, high sensitivity C-reactive protein.

Table 4. Carotid IMT and Femoral IMT in Association with Childhood Cancer Treatment

Dependent variables:	Natural logarithm of carotid IMT *			Natural logarithm of femoral IMT *		
Independent variables ¶:	B	95% CI	*P*-value	B	95% CI	*P*-value
Age at diagnosis (</≥ 4 years)	0.013	-0.018 – 0.045	.402	-0.012	-0.044 – 0.020	.457
Age at visit	0.009	0.007 – 0.011	**< .001**	0.009	0.007 – 0.011	**< .001**
Sex	-0.045	-0.070 – -0.020	**< .001**	-0.047	-0.072 – -0.022	**< .001**
Anthracyclines *(n=199)*	-0.036	-0.064 – -0.008	**.012**	-0.005	-0.034 – 0.023	.714
Cumulative dose of anthracyclines *(by 100 mg/m²)*	-0.009	-0.017 – -0.001	**.035**	-0.002	-0.010 – 0.006	.620
Platin *(n=22)*	-0.030	-0.075 – 0.015	.195	-0.024	-0.070 – 0.022	.302
Any chemotherapy *(n=249)*	-0.023	-0.065 – 0.019	.287	-0.013	-0.056 – 0.029	.537
Any radiation therapy *(n=174)*	0.028	0.002 – 0.054	**.036**	0.029	0.003 – 0.055	**.032**
Cranial-/craniospinal-irradiation *(n=102)*	0.014	-0.012 – 0.040	.295	-0.009	-0.036 – 0.017	.487
Irradiation of neck [1] *(n=50)*	0.048	0.016 – 0.080	**.003**	0.042	0.009 – 0.075	**.012**
Chest irradiation [2] *(n=53)*	0.060	0.029 – 0.091	**< .001**	0.026	-0.006 – 0.057	.115
Irradiation o fabdomen [3] *(n=51)*	0.034	0.002 – 0.065	**.035**	0.019	-0.013 – 0.051	.234
Total body irradiation *(n=17)*	-0.036	-0.087 – 0.016	.173	0.016	-0.036 – 0.068	.536

Note: [1], irradiation of neck includes neck, mantle field and/or spine; [2], chest irradiation includes mediastinum, mantle field, total lung and/or spine; [3], irradiation of abdomen includes abdomen, pelvic and/or spine; IMT, intima media thickness; CI, confidence interval; ¶, multivariate linear regression analysis with 'fixed' confounding variables 'age at diagnosis', 'current age' and 'sex'; **bold typed**, significantly associated with cancer treatment modality.

with previous TBI. PAI-I (B = 0.3; 95% CI 0.1-0.5; *P* = .011) and t-PA (B = 0.2; 95% CI 0.1-0.3; *P* = .003) were associated with any RT. hsCRP was associated with cranial-/craniospinal-RT (B = 0.4; 95% CI 0.04-0.71; *P* =.03) and the albumin/creatinine-ratio with platin exposure (B = 0.3; 95% CI 0.02-0.50; *P* = .035).

Vascular damage and cardiovascular risk factors (Table 5)

The occurrence of cardiovascular risk factors was compared between CCS with a carotid IMT ≥ 0.65 mm (≥ P^{75}) and CCS with a carotid IMT < 0.65 mm. In the adjusted logistic regression model, carotid IMT ≥ 0.65 mm was associated with hypertension, overweight, the metabolic syndrome and insulin/glucose-ratio. Femoral IMT ≥ 0.56 mm (≥ P^{75}) was associated with the metabolic syndrome. FMD ≤ 1.47% (≤ P^{25}) was not significantly associated with any of the cardiovascular risk factors (data not shown)

The occurrence of cardiovascular risk factors was compared between CCS with PAI-I

Table 5. Carotid IMT ≥ 0.65 mm and Femoral IMT ≥ 0.56 mm, and the Marker Proteins PAI-I antigen ≥ 27 ng/mL and t-PA ≥ 6.9 ng/mL in association with Cardiovascular Risk Factors

Dependent variables:	**Carotid IMT ≥ 0.65 mm ¶**		**Femoral IMT ≥ 0.56 mm ¶**		**PAI-I ≥ 27 ng/mL ¶**		**t-PA ≥ 6.9 ng/mL ¶**	
Independent variables ¶:	OR	95% CI (*P*- value)	OR	95% CI (*P*- value)	OR	95% CI (*P*-value)	OR	95% CI (*P*-value)
Age at diagnosis (</≥ 4 years)	2.9	1.0 – 8.8 (.060)	0.6	0.3 – 1.4 (.272)	0.84	0.39 – 1.81 (.648)	0.88	0.40 – 1.91 (.739)
Sex	0.4	0.2 – 0.9 **(.015)**	0.3	0.2 – 0.6 **(.001)**	1.32	0.74 – 2.34 (.350)	0.47	0.25 – 0.85 **(.013)**
Age at visit	1.2	1.1 – 1.2 **(< .001)**	1.2	1.1 – 1.3 **(< .001)**	1.08	1.04 – 1.14 **(.001)**	1.13	1.07 – 1.18 **(< .001)**
Hypertension	2.8	1.2 – 6.4 **(.018)**	1.6	0.7 – 3.5 (.279)	1.18	0.51 – 2.76 (.699)	4.36	1.86 – 10.24 **(.001)**
Hypercholesterolemia	0.9	0.4 – 1.8 (.740)	1.8	0.9 – 3.5 (.103)	1.65	0.86 – 3.14 (.131)	2.33	1.23 – 4.43 **(.010)**
Overweight	3.3	1.7 – 6.3 **(<.001)**	1.3	0.7 – 2.4 (.472)	3.21	1.76 – 5.85 **(< .001)**	6.22	3.27 – 11.84 **(< .001)**
Underweight	1.5	0.4 – 5.8 (.593)	1.4	0.4 – 5.6 (.600)	1.09	0.33 – 3.60 (.893)	0.62	0.15 – 2.49 (.498)
Current smoking	1.0	0.5 – 2.1 (.963)	1.2	0.6 – 2.4 (.665)	1.65	0.85 – 3.19 (.138)	0.80	0.40 – 1.61 (.537)
Metabolic syndrome	4.7	1.6 – 13.6 **(.004)**	2.8	1.0 – 7.7 **(.045)**	2.55	0.97 – 6.68 (.057)	9.93	3.00 – 32.87 **(< .001)**
Renal dysfunction	2.9	1.0 – 9.0 (.061)	0.6	0.2 – 2.2 (.434)	2.52	0.98 – 6.44 (.054)	1.42	0.52 – 3.88 (.493)
Albuminuria (≥ 30 mg/24-h)	1.4	0.5 – 4.1 (.499)	2.8	1.0 – 7.9 (.054)	1.02	0.34 – 3.04 (.978)	1.64	0.59 – 4.58 (.342)
Insulin/glucose-ratio	1.3	1.1 – 1.6 **(.005)**	1.1	0.9 – 1.3 (.318)	1.49	1.23 – 1.82 **(< .001)**	1.86	1.46 – 2.36 **(< .001)**
Homocysteine (µmol/L)	1.0	0.9 – 1.1 (.723)	1.0	1.0 – 1.1 (.202)	0.99	0.94 – 1.05 (.760)	0.96	0.89 – 1.03 (.245)

Note: ¶, reference value of variable ≥ P^{75}; IMT, intima media thickness; t-PA, tissue-type plasminogen activator; PAI-I, plasminogen activator inhibitor type 1; FMD, flow-mediated vasodilatation; OR, odds ratio; CI, confidence interval; ¶, multivariate logistic regression analysis with 'fixed' confounding variables 'age at diagnosis', 'current age' and 'sex'; **bold typed**, significantly associated with listed variable

≥ 27 ng/L (≥P^{75}; n = 68) and those with PAI-I below 27 ng/L, using the adjusted logistic regression model. PAI-I ≥ 27 ng/L was associated with overweight and a higher insulin/glucose-ratio, and tended to be associated with the metabolic syndrome. Using the same adjusted regression model, the cardiovascular risk factors between CCS with t-PA ≥ 6.9 ng/mL (≥P^{75}; n = 77) and those with t-PA below 6.9 ng/mL were compared. T-PA ≥ 6.9 ng/mL was associated with hypertension, hypercholesterolemia, overweight, the metabolic syndrome and a higher insulin/glucose-ratio.

Carotid IMT was not associated with endothelial or inflammatory marker proteins (data not shown). Femoral IMT was significantly associated with urinary albumin-excretion (B = 0.018; 95% CI 0.003-0.033; P = .016) and with albumin/creatinine-ratio (B = 0.025; 95% CI 0.001-0.050; P = .044).

DISCUSSION

This study shows that at median 18 years post-treatment, carotid IMT and femoral IMT were associated with previous RT, especially when RT was administered to the neck region. Compared with sibling controls, CCS had more often endothelial damage and an unfavorable cardiovascular risk profile. The prevalence of cardiovascular risk factors was higher in survivors with a high carotid and/or femoral IMT and/or high levels of the endothelial marker proteins PAI-I and t-PA.

Thus far, most studies on vascular damage after childhood cancer treatment were performed in small cohorts only addressing the association with previous RT [6,7]. These studies suggested that survivors treated with neck and/or cranial RT had a higher carotid IMT compared with healthy controls [6,7]. The current study comprised a much larger cohort of CCS (n = 277), who received a variety of treatment modalities, i.e. RT and/or chemotherapy. In the general population it has been shown that a higher carotid IMT represents structural atherosclerosis that predicts overt cardiovascular events [20]. Also femoral IMT is considered as an independent parameter to predict coronary artery disease [21,22]. In the current study, we assessed for the first time femoral IMT in CCS, which was interestingly associated with any type of RT, especially when given on the neck. This might suggest that RT-treated CCS are at risk for generalized coronary artery disease on the long run.

In the entire group of CCS, higher plasma PAI-I and t-PA levels were found compared with the controls. Moreover, CCS who received any type of RT had higher plasma PAI-I and t-PA levels, especially after previous TBI. Both PAI-I and t-PA have been described as marker proteins for endothelial damage and increased values have shown to be associated with a higher prevalence of coronary artery disease [23,24]. The association of earlier RT and the

existence of both vascular damage (i.e. a higher carotid and femoral IMT) and endothelial activation (i.e. increased plasma PAI-I and t-PA levels) suggests systemic vascular damage. We found no difference in FMD between CCS and controls and no association between FMD and any of the treatment modalities. However, the value of FMD in the assessment of coronary artery disease has been considered of less value than morphological parameters, such as IMT[25]. Other studies found abnormally increased endothelial marker proteins without abnormalities in FMD [26,27].

We observed no association between vascular damage and previous chemotherapy. Only urinary albumin/creatinine-ratio, considered as a parameter of glomerular function, was associated with previous platin-derivates. The number of platin-treated CCS in the current study was too small (n = 22) to draw definitive conclusions about the risk of endothelial damage after platin-treatment. However, in previous studies on vascular function in survivors of adult cancer, we revealed an association between platin-based chemotherapy and microalbuminuria [8,27]. In our study endothelial damage was not associated with earlier anthracycline exposure as measured in 277 CCS at median 18 years post-treatment. Only one small study in 14 anthracycline-treated CCS found endothelial dysfunction (measured by FMD) at a mean of 19.8 months post-treatment [10]. The much shorter follow-up after completion of cancer treatment impeded proper comparison with our study results.

In the current study, the prevalence of the metabolic syndrome and renal dysfunction was increased among CCS and there was a tendency of more hypertension. These symptoms are known to enhance cardiovascular risk [28-31]. The unfavorable cardiovascular risk profile found in CCS was especially evident in survivors with a higher carotid and/or femoral IMT and in those with higher plasma levels of PAI-I and/or t-PA. In the general population, young adults with cardiovascular risk factors are at risk for a higher carotid IMT, especially when they have signs of endothelial damage [32]. This is the first study in CCS that assessed the association between cardiovascular risk factors and vascular and endothelial damage. Our results suggest that cardiovascular risk factors play an important role in the development of precocious atherosclerosis after cancer treatment and possibly in the long run in the development of overt cardiovascular events. This hypothesis needs further exploration in a longitudinal prospective study with serial assessments of cardiovascular risk factors, endothelial marker proteins and parameters of vascular structure.
The strengths of our study are the large sample size, the extended follow-up and the large number of sibling controls. Until now, most studies on vascular damage in CCS determined vascular function (FMD), vascular structure (carotid as well as femoral IMT) or inflammatory and endothelial marker proteins, while in the current study we assessed all entities. A limitation of our study is the heterogeneity of the cohort.

We conclude that CCS treated with potentially cardiovascular-toxic cancer treatment have an increased risk of endothelial damage and a higher prevalence of cardiovascular risk factors compared with controls. Endothelial damage and a higher carotid and femoral IMT are associated with previously given RT, especially when administered to the neck.

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CHAPTER 8

SUMMARY AND FUTURE PERSPECTIVES

The overall 5-year survival of childhood cancer survivors (CCS) raised from less than 25% in the 60s to 70% in the 90s [1]. This substantial improvement in survival results in an enormously increasing number of long-term CCS, who are at risk to develop some kind of late effect. Studies performed in long-term survivors of childhood cancer showed a wide variety of possible late complications [2,3]. Five or more years after completion of cancer treatment mortality rates in CCS are still higher compared with controls [4,5]. Cardiac failure has been described as one of the leading causes of death in CCS [6]. While clinical cardiovascular late complications after childhood cancer treatment have been widely described [6,7], the prevalence of subclinical cardiac and/or vascular damage is almost unknown and has found to be up to 57% [8]. Early detection of subclinical cardiac and/or vascular damage and potentially associated risk factors may enable development of intervention strategies with the aim to prevent or ameliorate development of clinical cardiovascular disease.

The aim of this thesis was to assess the prevalence of clinical and subclinical cardiac and/or vascular disease and cardiovascular risk factors in survivors of childhood cancer treated with the potentially cardiovascular-toxic anthracyclines, platin-derivates and/or radiotherapy.

Abnormal body composition after childhood cancer treatment

An abnormal body composition, especially overweight/obesity, has been described in association with abnormal metabolic and inflammatory profiles and subsequently with an increased risk to develop cardiovascular disease [9,10]. The mortality risk (overall as well as cardiovascular) is increased in persons with overweight as well as in those with underweight [11]. As survivors of childhood cancer may already be at risk for cardiovascular disease due to the previous treatment, assessment of the risk of an abnormal body composition in association with specific cancer treatment might be especially important to enable preventive measures. Therefore, in **chapter 2**, an overview was given on the available studies in the literature on changes in body composition after previous childhood cancer treatment. Firstly, several methods in analysis of body composition have been discussed. The most commonly used method in assessment of body composition is by calculating the body mass index (BMI; weight (kg)/ height^2 (m)). A disadvantage of using BMI is that changes in BMI are not always related to changes in percentage body fat, especially in persons who have a high volume of lean body mass. Despite this disadvantage, BMI is widely used in studies performed in CCS as it is easily calculated. In the general population, BMI is a known predictor of metabolic health risk [12]. Prognostic value of other methods in analysis of body composition, such as dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA), are not yet established. In chapter 2 it was described that the use of a combination of several methods in measuring body composition seems to be

most appropriate. Subsequently, chapter 2 summarizes the development of overweight/obesity and underweight in association with previous cancer treatment. Survivors who received cranial/craniospinal-irradiation (CRT) had an increased prevalence of obesity, shortly after completion of cancer treatment and/or many years post-treatment. Survivors after corticosteroid treatment have a higher prevalence of obesity during the first years post-treatment, while the long-term effects are not yet known. On the other hand, the risk of developing underweight has been described in association with previous treatment with alkylating agents and/or anthracyclines. Studies on the association between other cytotoxic treatment and body composition are not available. Finally, in chapter 2 the possible underlying mechanisms in the development of underweight/overweight in CCS were described. Little is known about the underlying mechanisms of development of underweight in CCS. It has been found that the majority of survivors with underweight (> 70%) had an underlying medical problem and/or were identified as current smokers [13]. On the other hand, the mechanisms that may play a role in the development of overweight/obesity in CCS have been more extensively studied. An important theory is that of a disturbed energy balance, which may result from a reduced physical activity/energy expenditure and/or an increased energy intake. A disturbed energy balance has been described in association with hypothalamic damage, caused by CRT or cranial surgery. Other mechanisms that may play a role are a younger age of the adiposity rebound (i.e. the increase in BMI that occurs after a nadir observed in children, normally around the age of 5.5 years), growth hormone deficiency and gonadal dysfunction. The conclusion of chapter 2 was that there are no unambiguous data available on the underlying mechanisms and on the timing of change in body composition after childhood cancer treatment.

In **chapter 3**, the results of a longitudinal retrospective study on BMI change in CCS were described. Three hundred seventy-seven survivors of childhood cancer treated with potentially cardiovascular-toxic cancer treatment (i.e. anthracyclines, platin-derivates and/or radiotherapy) were included in this study. BMI was calculated at diagnosis and at several time-points after completion of cancer treatment. After reaching final height (≥ 5 years post-treatment), the prevalence of underweight was higher in the survivors compared with a reference population. Survivors who received a higher cumulative anthracycline dose were found to have a lower rate of annual BMI increase from completion of cancer treatment until reaching final height, and were more underweight at final height. In addition, survivors who received total body irradiation tended to have a lower BMI at completion of cancer treatment ($P = .06$), while BMI increase afterwards until reaching final height was similar between survivors with or without total body irradiation. The lower BMI at completion of treatment was reflected in more underweight at final height in those who received total body irradiation. The prevalence of overweight at final height

in the whole group of CCS compared with the reference population was not significantly different. However, specification according to the previously given cancer treatment showed that survivors who received CRT had a higher BMI at completion of cancer treatment compared with CCS who received no CRT. This is reflected in more overweight at final height. In addition, survivors who received a CRT-dose ≥30 Gy had the highest risk of overweight at final height, which may be the resultant of the higher BMI at completion of cancer treatment and a higher BMI increase post-treatment until reaching final height.

To gain further insight in the explanation of an abnormal body composition after childhood cancer treatment, exploration by biochemical and genetic determinants may be worthwile. Leptin is an adipocyte-secreted hormone and can circulate in the plasma free or bound to the associated receptor (LEPR). The LEPR is located in the hypothalamus and amongst others in the adipose tissue [14]. Leptin has been described as involved in body weight regulation [15] and a higher leptin level is associated with a higher amount of stored fat [14]. Resistance to leptin has been proposed as potential mechanism for the development of obesity. A genetic defect in the LEPR may lead to leptin resistance and cause obesity with high serum leptin levels. Until now, only one study in CCS found a genetic LEPR-variation (LEPR Gln Arg polymorphism) in association with an increased susceptibility to develop obesity after treatment for acute lymphoblastic leukemia [16]. Therefore, it would be of interest to measure leptin levels and the genetic LEPR-variation in our cross-sectional cohort of 277 CCS and to assess the association with the prevalence of under-/overweight in adulthood.

Cardiac complications after childhood cancer treatment

In the **chapters 4, 5 and 6** of this thesis, the cardiac function of CCS has been described. Longitudinal prospective studies on cardiac function in CCS are scarce and have a follow-up up to 17 years post-treatment [17-19]. In the chapters 4 and 5, the results of two prospective studies performed in very long-term survivors of a malignant bone tumor and acute lymphoblastic leukemia, respectively, were shown. Results of the first prospective study performed in medium to high dose doxorubicin-treated bone tumor survivors (median anthracycline dose 360 mg/m^2; range 225-550) showed progressive cardiac dysfunction **(chapter 4)**. The 22 included survivors received three consecutive cardiac assessments at median 9, 14 and 22 years after completion of cancer treatment. At the last assessment at median 22 years post-treatment, the prevalence of systolic as well as diastolic dysfunction (27% and 45%, respectively) was found to be higher compared with the previously performed assessment at median 14 years post-treatment (9% and 18%, respectively). Also heart rate variability showed further deterioration over time, suggesting autonomic cardiac dysfunction. So, even decades after finishing cancer treatment cardiac dysfunction

may be newly developed or become overt.

In **chapter 5** the results of a prospective cardiac study performed in survivors of childhood acute lymphoblastic leukemia treated with low-dose daunorubicin (100 mg/m^2) was shown. Median 22 years (range 19.5-24.5) after completion of cancer treatment, neither cardiac abnormalities nor autonomic cardiac dysfunction were found. In addition, no significant deterioration of cardiac function (measured by shortening fraction and E/A-ratio) was detected as compared with results of a cardiac assessment performed in the same CCS at median 12 years post-treatment. To establish if daunorubicin dose up to 100 mg/m^2 is safe, the results of this study need to be confirmed in a larger study.

Wall motion score index (WMSI) has been described as load-independent parameter (that is independent of left ventricle filling) in the assessment of systolic function. Thus far, most studies on systolic cardiac function in CCS were performed with the analysis of shortening fraction, which is a load-dependent parameter. In the assessment of diastolic function most studies rely on the load-dependent parameter E/A-ratio (that is mitral valve inflow velocities in early (E) and late (A) diastole). However, Tissue Velocity Imaging of early diastole (TVI Et) is currently considered as the most reliable and load-independent parameter in the measurement of diastolic function. The advantage of load-independent parameters is their lower intra- and inter-individual variation. In the cross-sectional cardiac study described in **chapter 6**, both WMSI and TVI Et were used as parameters for respectively systolic and diastolic dysfunction. In total, 277 CCS and 130 sibling controls were recruited. Survivors were included on the base of their potentially cardiovascular-toxic cancer treatment (i.e. anthracyclines, platin-derivates and/or radiotherapy). If survivors received both doxorubicin and daunorubicin as part of their cancer treatment, the cumulative doses of doxorubicin and daunorubicin were added as they were considered equal in toxicity. It was shown that systolic (WMSI >1.00; 15% in CCS vs. 2% in controls) and diastolic dysfunction (TVI Et < 8.00 cm/sec; 12% in CCS vs. 1% in controls) are important as late complications of childhood cancer treatment. Systolic dysfunction was found to be associated with a higher cumulative dose of anthracyclines, not with chest irradiation. Diastolic dysfunction was associated with a cumulative dose of anthracyclines > 225 mg/m^2 and with chest irradiation, especially when radiotherapy was given on the mediastinum.

It follows from the studies described in chapters 4 till 6 that continued cardiac follow-up in CCS treated with anthracyclines and/or chest irradiation is warranted. In addition, it would be worthwile to evaluate treatment with cardioactive medication, such as ACE-inhibitors or ß-blockers, on the course of cardiac dysfunction. Until now, most studies

on cardiac function in CCS focus on systolic function only. The results of our cardiac studies indicate that diastolic dysfunction is as prevalent as systolic dysfunction in CCS and that diastolic dysfunction is frequently occurring without systolic dysfunction. The clinical implications of subclinical (isolated) diastolic dysfunction in long-term CCS still have to be established. In our hospital, patients with diastolic dysfunction receive regular follow-up by echocardiography and more aggressive treatment of coexistent cardiovascular risk factors, such as hypertension. In the future, a longitudinal prospective study with serial echocardiography from diagnosis would be of interest. In addition to the echocardiography methods described in the studies of this thesis, 'strain rate imaging' could be measured, which probably is a refinement in the assessment of left ventricular function by echocardiography [20,21]. Other methods to assess cardiac function are magnetic resonance imaging (MRI) or CT scan with coronary artery calcification score. Both cardiac MRI and CT enable more detailed information about cardiac function as compared with echocardiography, especially in the detection and evaluation of coronary artery disease.

Vascular dysfunction and cardiovascular risk factors after childhood cancer treatment

Studies on vascular function in CCS are scarce and mostly performed in small cohorts of survivors who received cranial and/or neck irradiation [22,23]. In survivors of adult testicular cancer, previously treated with platin-derivates, vascular structure and endothelial markers were studied shortly after completion of cancer treatment and showed a higher intima media thickness (IMT) of the carotid artery as compared with carotid IMT before cancer treatment [24]. In the cohort of 277 CCS and 130 sibling controls described in chapter 6, the vascular function and structure (dynamical and biochemical) and potentially associated cardiovascular risk factors were assessed (**chapter 7**). Both an increased carotid and/or femoral IMT and endothelial damage have been described as key variables in the pathogenesis of (early signs of) atherosclerosis and its associated complications, such as stroke or cardiovascular disease [25-28]. In chapter 7, IMT of the vascular wall of the carotid and femoral artery were measured by ultrasound. For the entire group of CCS, no difference in carotid and femoral IMT was found as compared with the controls. However within the group of CCS, both carotid and femoral IMT were significantly associated with previously given neck irradiation. The CCS had an unfavorable cardiovascular risk profile (i.e. metabolic syndrome, renal dysfunction and a higher ratio of total cholesterol/ HDL-cholesterol) compared with the controls. Especially those with a carotid IMT above the 75th percentile were more frequently diagnosed with hypertension, overweight and/or the metabolic syndrome and/or had a higher insulin/glucose-ratio. A femoral IMT above the 75th percentile was associated with an increased prevalence of the metabolic syndrome. Endothelial and inflammatory marker proteins (such as plasminogen activator inhibitor

type 1 antigen (PAI-I) and tissue-type plasminogen activator antigen (t-PA) were also measured in the CCS and the controls. The CCS had a significantly higher PAI-I and t-PA compared with the controls, indicating endothelial damage. Higher values of PAI-I and t-PA were associated with previously given radiotherapy. The CCS who had values of PAI-I and/or t-PA above the 75th percentile had a worse cardiovascular risk profile compared with those with values below the 75th percentile. Concluding from chapter 7, CCS after previous radiotherapy (any type of irradiation, but especially when given on the neck) had an increased carotid and femoral IMT and more signs of endothelial damage. A higher IMT and endothelial damage were associated with an unfavorable cardiovascular risk profile.

In the general healthy population, a higher prevalence of cardiac dysfunction, especially diastolic dysfunction, and vascular damage have been described in association with advanced age [29,30]. It has been suggested that free oxygen radicals play an important role in the normal aging process and that an overload of free oxygen radicals may lead to precocious aging [31]. Chemotherapy and radiotherapy induce their anti-cancer effect by the release of free oxygen radicals. As showed in this thesis, survivors of cancer had an increased prevalence of cardiac dysfunction and vascular damage, which may indicate a pattern of precocious aging. Probably, precocious aging in CCS is initiated by an access and accumulation of free oxygen radicals, e.g. oxidative stress, after previously given cancer treatment. This hypothesis needs to be established. Recently, Advanced Glycation Endproducts (AGEs) were recognized as parameters of oxidative stress [32]. They may serve as potential early markers of preclinical cardiac dysfunction and/or atherosclerosis [32].

Conclusion and future perspectives

The studies in this thesis show that there is a high prevalence of cardiac and vascular damage and a higher prevalence of cardiovascular risk factors in CCS compared with healthy controls. Especially the occurrence of (isolated) diastolic dysfunction, and the relation between vascular and endothelial damage, cardiovascular risk factors and their relation to one another deserves further attention in future research. Firstly, continued cardiac and/or vascular evaluation of the 277 CCS is warranted to enable prospective insights in the development of subclinical/clinical cardiovascular damage, but it can also be used for individual patient-related risk assessment. Future research must include the most up-to-date methods in cardiovascular risk assessment (for example, strain echocardiography and/or determination of AGEs) and also an exploration of genetic polymorphisms. Genetic determinants may play an important role as results from the current cross-sectional study indicate that not all CCS treated with the same dosage schedules develop the same degree of cardiovascular damage and risk factors. Furthermore, to gain insight in the underlying pathophysiological mechanisms and relations between cardiovascular risk factors and the

development of cardiovascular damage, follow-up of newly diagnosed childhood cancer patients should be performed from diagnosis.

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CHAPTER 9

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Gedurende de laatste decennia is het aantal overlevenden van kinderkanker sterk toegenomen. Bij kinderen die tussen 1960-1969 met kanker werden gediagnosticeerd was de gemiddelde 5-jaars overleving minder dan 25%, terwijl deze bij diagnose in de jaren negentig gemiddeld 70% was. De verbetering in overleving zorgt voor een stijging in het absolute aantal lange-termijn overlevenden van kinderkanker. Hiermee worden echter ook de mogelijke late complicaties ten gevolge van de vroegere kinderkankerbehandeling duidelijker. Uit eerder onderzoek is gebleken dat er een grote variatie aan mogelijke late gevolgen bestaat en dat meer dan 5 jaar na voltooiing van de kankerbehandeling de mortaliteit nog steeds significant hoger is dan bij gezonde leeftijdsgenoten. Eén van de belangrijkste oorzaken is het optreden van klinische cardiale schade, hetgeen in diverse studies als late complicatie van de kinderkankerbehandeling is beschreven. Ter preventie van klinische cardiovasculaire schade lijkt vroege detectie van subklinische schade en mogelijk geassocieerde cardiovasculaire risicofactoren vereist om tijdig interveniërende behandeling in te stellen. Het **doel van dit proefschrift** is het verkrijgen van inzicht in de prevalentie van klinische en subklinische cardiale en/of vasculaire schade en cardiovasculaire risicofactoren in overlevenden van kinderkanker die voorheen werden behandeld met de potentieel cardiovasculair-toxische anthracyclines, platinum en/of radiotherapie.

Onder- of overgewicht na behandeling voor kinderkanker

In de algemene populatie is een afwijkende lichaamssamenstelling, zowel onder- als overgewicht, beschreven in associatie met abnormale metabole en inflammatoire profielen en hiermee met een verhoogd risico op het ontwikkelen van cardiovasculaire ziekte. Aangezien overlevenden van kinderkanker al een verhoogd risico op cardiovasculaire ziekte hebben ten gevolge van de potentieel cardiotoxische kankerbehandeling, is inzicht in de lichaamssamenstelling van belang om zonodig preventieve maatregelen te treffen. In **hoofdstuk 2** van dit proefschrift wordt een overzicht gegeven van de tot dan toe beschikbare studies in de literatuur met betrekking tot veranderingen in lichaamssamenstelling na vroegere kinderkankerbehandeling. Allereerst worden de verschillende methoden voor het analyseren van de lichaamssamenstelling besproken. De meest gebruikte methode om de lichaamssamenstelling weer te geven is door middel van het berekenen van de 'body mass index' (BMI; gewicht (kg)/ lengte^2 (m)). Een nadeel van het gebruik van de BMI is dat veranderingen in BMI niet altijd goed relateren met de verandering in percentage lichaamsvet. Dit is bijvoorbeeld het geval bij mensen met een relatief hoog vetvrij lichaamsgewicht (de zogenaamde 'lean body mass'). Ondanks dit nadeel wordt BMI in de meeste studies gebruikt, aangezien het makkelijk is om te bepalen, en BMI is beschreven als een significante voorspeller van het metabole gezondheidsrisico. Andere methoden voor het bepalen van de lichaamssamenstelling zijn de DEXA-scan

('dual energy X-ray absorptiometry') en de BIA ('bioelectrical impedance analysis'). Echter van deze methoden is de prognostische waarde nog niet eenduidig vastgesteld. Aanbevolen wordt om bij voorkeur een combinatie van verschillende methoden te gebruiken. Vervolgens wordt in hoofdstuk 2 de beschikbare kennis samengevat op het gebied van een afwijkende lichaamssamenstelling na behandeling voor kinderkanker. Uit verschillende studies komt naar voren dat patiënten die behandeld zijn met craniale/craniospinale-as bestraling (CRT) een significant hogere prevalentie obesitas hebben ten opzichte van degenen die deze behandeling niet kregen. Dit blijkt het geval te zijn zowel kort na de behandeling alsook vele jaren na voltooiing van de behandeling. Ook patiënten die werden behandeld met corticosteroïden hebben een hogere prevalentie obesitas in de eerste jaren na voltooiing van de kankerbehandeling. Over het langetermijn effect van corticosteroïden is tot dusverre nog weinig bekend. Wat betreft het risico op het ontwikkelen van ondergewicht na eerdere kankerbehandeling is in één studie een associatie met alkylerende middelen en/of anthracyclines beschreven. Over de andere cytostatica is in de literatuur nog weinig bekend. In hoofdstuk 2 wordt ten slotte besproken welke mechanismen ten grondslag kunnen liggen aan het ontstaan van onder-/overgewicht na vroegere kankerbehandeling. Er blijkt tot nu toe weinig bekend over de mechanismen in de ontwikkeling van ondergewicht. Roken en onderliggende medische problemen worden als bijkomende factoren beschreven. Ook over mechanismen die mogelijk een rol spelen in de ontwikkeling van overgewicht bestaan nog veel vragen die beantwoording behoeven. Eén van de belangrijkste theorieën terzake is dat sprake zou zijn van een verstoorde energiebalans, hetgeen veroorzaakt kan worden door een verminderd fysiek actief zijn en/of een toegenomen energie inname. Deze verstoorde energiebalans is beschreven in associatie met hypothalame schade veroorzaakt door behandeling met CRT en/of hersenchirurgie. Andere beschreven mechanismen waardoor overgewicht zou kunnen ontstaan, zijn (1) een vroege adipositas rebound (dat wil zeggen voor het 5e levensjaar); (2) groeihormoondeficiëntie en (3) gonadale dysfunctie. Op grond van deze bevindingen doen wij de aanbeveling in hoofdstuk 2 voor het uitvoeren van een longitudinale prospectieve studie in een groter cohort kinderkankeroverlevenden ten einde een betere inschatting te kunnen maken wat betreft de prevalentie van een afwijkende lichaamssamenstelling in samenhang met de gegeven kankerbehandelingen. Er blijkt nog veel onduidelijkheid te bestaan over het moment van ontstaan van onder-/overgewicht na eerdere kankerbehandeling. Ook dit zou verduidelijkt kunnen worden door middel van longitudinaal prospectief onderzoek.

Enkele conclusies die staan geformuleerd in hoofdstuk 2 zijn verder uitgewerkt in een longitudinale retrospectieve studie, waarvan de resultaten zijn beschreven in **hoofdstuk 3**. Het doel van deze studie was allereerst het bepalen van de prevalentie van onder-

en overgewicht na het bereiken van de eindlengte in lange-termijn overlevenden van kinderkanker die behandeld werden met potentieel cardiovasculair-toxische middelen (anthracyclines, platinum en/of radiotherapie). Het tweede doel was het bepalen van het BMI-beloop vanaf de voltooiing van de kankerbehandeling tot aan het bereiken van de eindlengte in relatie tot de verschillende kankerbehandelingen. In totaal werden 377 overlevenden van kinderkanker geïncludeerd. BMI werd berekend bij diagnose en op verschillende tijdstippen na voltooiing van de kankerbehandeling. Na het bereiken van de eindlengte (5 jaar of langer na voltooiing van de behandeling) werd een hogere prevalentie ondergewicht gevonden in de totale groep overlevenden ten opzichte van een gezonde referentiepopulatie (14% vs. 4%). Overlevenden die een hogere cumulatieve dosis anthracyclines ontvingen lieten een mindere snelle BMI-stijging zien vanaf voltooiing van de behandeling tot aan het bereiken van de eindlengte ten opzichte van degenen die geen of een lagere dosis anthracyclines kregen. Dit uitte zich in meer ondergewicht na het bereiken van de eindlengte bij degenen behandeld met een hogere dosis anthracyclines (per 100 mg/m^2 hogere dosis anthracyclines, 1,3 maal hogere kans op ondergewicht). Overlevenden die behandeld werden met totale lichaamsbestraling neigden naar het hebben van een lagere BMI direct na voltooiing van de kankerbehandeling (P = 0,06), terwijl de BMI-stijging daarna tot aan het bereiken van de eindlengte niet significant verschilde ten opzichte van degenen zonder totale lichaamsbestraling. De lagere BMI direct na voltooiing van de behandeling resulteerde in significant meer ondergewicht na het bereiken van de eindlengte in overlevenden die behandeld waren met totale lichaamsbestraling. De prevalentie overgewicht bleek niet significant verschillend in de totale groep overlevenden ten opzichte van de referentiepopulatie (19% vs. 22%). Echter, overlevenden die behandeld waren met CRT lieten een significant hogere BMI zien direct na voltooiing van de behandeling ten opzichte van degenen die geen CRT kregen. Dit kwam tot uitdrukking in meer overgewicht bij het bereiken van de eindlengte. Voorts bleken degenen die bestraald werden met 30 Gy of meer het hoogste risico te hebben op het ontwikkelen van overgewicht na het bereiken van de eindlengte. Dit is waarschijnlijk het resultaat van een significant hogere BMI direct na voltooiing van de behandeling en een snellere jaarlijkse BMI-stijging daarna in overlevenden behandeld met ≥30 Gy CRT.

Cardiale complicaties na vroegere kinderkankerbehandeling

Cardiale afwijkingen kunnen vele jaren na de behandeling voor kinderkanker optreden. Bestaande studies naar cardiale late effecten zijn vooral gericht op klinisch hartfalen en daarbij wordt vooral aandacht geschonken aan de systolische cardiale functie. Uit onderzoek verricht in de algemene populatie is echter gebleken dat naast de systolische ook de diastolische functie van belang is, aangezien beiden onafhankelijk van elkaar kunnen leiden tot klinisch hartfalen. Longitudinale prospectieve cardiale studies in overlevenden

zijn tot dusverre schaars en hebben een follow-up van maximaal 17 jaar na voltooiing van de kankerbehandeling. In **hoofdstuk 4** wordt een prospectieve cardiale studie beschreven uitgevoerd in 22 lange-termijn overlevenden van een maligne bottumor, die onder andere behandeling met het anthracycline-derivaat doxorubicin ontvingen. De dosering doxorubicin varieerde tussen de 225 en 550 mg/m^2 (mediaan 360 mg/m^2). Na twee eerdere cardiale onderzoeken in 1992 en 1997 (mediane follow-up respectievelijk 9 en 14 jaar), werd in 2004 een derde hartonderzoek uitgevoerd bestaande uit echocardiografie en 24-uurs ECG. Mediaan 22 jaar na voltooiing van de kankerbehandeling vonden we een significante verslechtering van de hartfunctie ten opzichte van het eerdere hartonderzoek verricht in 1997. Bij 27% van de patiënten werd systolische dysfunctie gevonden en bij 45% diastolische dysfunctie, terwijl dit bij het onderzoek in 1997 respectievelijk 9% (P = 0,02) en 18% (P = 0,02) was. Ook waren er aanwijzingen voor een verslechtering van de variabiliteit in hartactie, hetgeen wijst op autonome cardiale dysfunctie. Conclusie van dit onderzoek is dat na zeer langdurige cardiale follow-up in patiënten behandeld met gemiddelde tot hoge dosis doxorubicine progressieve verslechtering van de hartfunctie kan optreden.

De resultaten van een tweede prospectieve cardiale studie in overlevenden van acute lymfatische leukemie op de kinderleeftijd (n=23) zijn beschreven in **hoofdstuk 5**. Als vervolg op een eerder hartonderzoek in deze groep, uitgevoerd in 1995 (mediane follow-up 12 jaar), werd in 2005 een tweede hartonderzoek verricht. Het hartonderzoek bestond uit echocardiografie en een 24-uurs ECG, en vond gemiddeld 22 jaar na voltooiing van de kinderkankerbehandeling plaats. Alle patiënten werden behandeld met schedelbestraling en een aantal (n=13) ontving tevens een lage dosis van het anthracycline-derivaat daunorubicine (totale cumulatieve dosis: 100 mg/m^2). We vergeleken de resultaten van de groep patiënten behandeld met daunorubicine met de resultaten van degenen die geen daunorubicine kregen en met de resultaten van het hartonderzoek verricht in 1995. We vonden bij geen van de 23 patiënten cardiale afwijkingen of aanwijzingen voor autonome cardiale dysfunctie en de hartfunctie van de daunorubicine-behandelde patiënten was niet significant verslechterd ten opzichte van het eerdere hartonderzoek. Conclusie van dit onderzoek was dat na langdurige cardiale follow-up bij patiënten behandeld met een lage dosis daunorubicine voor acute lymfatische leukemie geen klinisch relevante cardiale verslechtering had plaatsgevonden. In een grotere trial zal bevestigd moeten worden of anthracyclines in een dosering van 100 mg/m^2 daadwerkelijk veilig zijn.

In **hoofdstuk 6** zijn de resultaten van een grotere cross-sectionele cardiale studie beschreven, waarbij gebruik wordt gemaakt van geavanceerde echocardiografische technieken. De 'wall motion score index' (WMSI) wordt beschreven als een parameter voor

het bepalen van de systolische cardiale functie en is onafhankelijk van de linker ventrikel vullingsdruk. Ook voor de bepaling van de diastolische cardiale functie is gebruik gemaakt van een vullings-onafhankelijke parameter, namelijk de 'tissue velocity imaging of early diastole' (TVI Et). In totaal werden 277 overlevenden van kinderkanker (5 jaar of langer na voltooiing van de kankerbehandeling en behandeld met anthracyclines, platinum en/of radiotherapie) en 130 controlepersonen (broers en zussen van de patiënten; gemiddelde leeftijd 26 jaar (range 18-51) opgeroepen voor een uitgebreid cardiovasculair onderzoek. De overlevenden waren gemiddeld 9 jaar (range 0-20) bij het stellen van de diagnose en 28 jaar (range 18-48) ten tijde van het onderzoek. Het hartonderzoek bestond uit echocardiografie (bepalen van systolische en diastolische parameters), ECG, baroreflex gevoeligheidsmeting (bepalen van de autonome cardiale functie) en meting van N-terminal pro-brain natriuretic peptide. Na een gemiddelde follow-up na voltooiing van de kankerbehandeling van 18 jaar werd bij 15 (5%) overlevenden van kinderkanker klinisch hartfalen (WMSI ≥1,50 en/of gebruik van medicatie voor hartfalen) vastgesteld. De prevalentie systolische dysfunctie (WMSI >1,00) in de overlevenden was significant hoger dan die in de controlepersonen (15% vs. 2%). Systolische dysfunctie bleek geassocieerd met een hogere cumulatieve dosis anthracyclines, maar niet met thoracale bestraling. De prevalentie diastolische dysfunctie (TVI Et <8,00 cm/sec) in overlevenden was ook significant hoger in de overlevenden in vergelijking met de controlepersonen (12% vs. 1%). Diastolische dysfunctie bleek geassocieerd met een cumulatieve dosis anthracyclines boven 225 mg/m^2 en met thoraxbestraling, vooral indien de bestraling werd gegeven specifiek op het mediastinum. Concluderend, na behandeling met potentieel cardiotoxische kankerbehandeling werd bij 23% van de lange-termijn overlevenden systolische en/of diastolische cardiale dysfunctie vastgesteld. Anthracycline-dosis en thoraxbestraling zijn risicofactoren voor het ontwikkelen van diastolische dysfunctie. De resultaten beschreven in de hoofdstukken 4, 5 en 6 laten zien dat diastolische dysfunctie veel frequenter voorkomt bij kinderkankeroverlevers dan gedacht. Dit is van belang omdat in de algemene populatie diastolische dysfunctie is beschreven als onafhankelijke prognostische factor in de ontwikkeling van hartfalen.

Vasculaire functie en cardiovasculaire risicofactoren na behandeling voor kinderkanker

Studies die de vasculaire functie hebben beschreven in overlevenden van kinderkanker zijn schaars en veelal uitgevoerd in kleine cohorten van overlevenden die voorheen behandeld waren met schedel- en/of halsbestraling. In **hoofdstuk 7** worden de resultaten van de vasculaire metingen beschreven, uitgevoerd in 277 overlevenden van kinderkanker (5 jaar of langer na voltooiing van de kankerbehandeling) en in 130 controlepersonen. De intima media dikte (IMT) van zowel de arteria carotis als ook de arteria femoralis is in andere

studies (in de algemene populatie) beschreven als een belangrijke factor in de pathogenese van arteriosclerose en de daarmee geassocieerde complicaties, zoals een beroerte of andere cardiovasculaire ziekten. In de studie beschreven in hoofdstuk 7 vonden wij geen verschil in carotis en femoralis IMT tussen de totale groep kinderkankeroverlevers en de controlepersonen. Echter, zowel carotis als femoralis IMT waren significant geassocieerd met eerder gegeven radiotherapie, vooral indien de radiotherapie werd gegeven op de hals. Voorts worden in hoofdstuk 7 ook de resultaten van endotheliale en inflammatoire marker eiwitten (zoals plasminogen activator inhibitor type 1 antigen (PAI-I) en tissue-type plasminogen activator antigen (t-PA)) beschreven. Kinderkankeroverlevers bleken een significant hoger PAI-I en t-PA te hebben in vergelijking met controlepersonen, hetgeen wijst op endotheliale schade. Hogere waarden van PAI-I en t-PA waren geassocieerd met de eerder gegeven radiotherapie. Een hogere carotis IMT, femoralis IMT, PAI-I en t-PA zou mogelijk kunnen duiden op een gegeneraliseerde endothelitis na vroegere radiotherapie. Verder bleken overlevenden van kinderkanker een nadelig cardiovasculair risicoprofiel te hebben ten opzichte van de controlepersonen. Dit uitte zich in een hogere prevalentie van het metabole syndroom, nierdysfunctie en een hogere ratio totaal cholesterol/ HDL-cholesterol. Bovendien hadden de overlevenden met een carotis IMT, femoralis IMT, PAI-I en/of t-PA $\geq 75^{e}$ percentiel meer cardiovasculaire risicofactoren dan degenen met waarden beneden de 75^{e} percentiel. Ter voorkoming van symptomatisch cardiovasculair lijden lijkt vroege detectie, en eventueel behandeling, van cardiovasculaire risicofactoren essentieel. Dat geldt in het bijzonder voor degenen die behandeld werden met radiotherapie (meer speciaal indien halsbestraling werd gegeven) en als IMT en/of marker eiwitten verhoogd zijn.

Conclusie en toekomstperspectieven

De studies beschreven in dit proefschrift geven een hoge prevalentie cardiale en vasculaire schade en cardiovasculaire risicofactoren aan in overlevenden van kinderkanker in vergelijking met gezonde controlepersonen. Vooral de bevindingen van een hoge prevalentie diastolische dysfunctie, en het optreden van vasculaire en endotheliale schade, cardiovasculaire risicofactoren en hun onderlinge relaties vereisen verder onderzoek. Voorts verdient het aanbeveling om het huidige cohort van 277 kinderkankeroverlevers te blijven vervolgen om zo prospectieve data te verzamelen. Op deze wijze kan meer inzicht worden verkregen in de ontwikkeling van subklinische en klinische cardiovasculaire schade. Hierin zal ook aandacht moeten zijn voor genetische factoren, want patiënten met dezelfde behandelschema's laten soms zeer verscheidene cardiovasculaire risicoprofielen zien. Ten slotte zou het opzetten van een prospectieve longitudinale studie naar cardiovasculaire schade en geassocieerde risicofactoren vanaf start van de kankerbehandeling nuttig kunnen zijn. Daarmee kan meer inzicht worden

verkregen in de onderliggende pathofysiologische mechanismen, waardoor wellicht in de toekomst betere behandelingen en preventieve maatregelen kunnen worden ontwikkeld.

LIST OF ABBREVIATIONS

AGEs	Advanced Glycation Endproducts
ALL	Acute lymphoblastic leukaemia
AR	Adiposity rebound
AV-block	Atrio-ventricular block
AVGNN	Average of all NN-intervals (in heart rate variability measurements)
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BRS	Baroreflex sensitivity
BSA	Body surface area
CCS	Childhood cancer survivors
CCSS	Childhood Cancer Survivor Study
CI	Confidence interval
CRF	Cardiovascular risk factors
CRT	Cranial/ craniospinal irradiation
DCLSG	Dutch Childhood Leukaemia Study Group
DEXA	Dual energy X-ray absorptiometry
DNR	Daunorubicin
E/A ratio	Ratio of mitral valve inflow velocities in early (E) and late (A) diastole
ECG	Electrocardiograph
E/E'-ratio	Ratio of mitral valve inflow velocity in early diastole (E) and Tissue Velocity Imaging of early diastole (TVI Et)
ELISA	Enzyme-Linked Immuno Sorbent Assay
FMD	Flow-mediated vasodilatation
FUP	Follow-up period
GHD	Growth hormone deficiency
GH	Growth hormone
Gy	Gray
HDL	High density lipoprotein
HF	High frequency power (in heart rate variability measurements)
HRV	Heart rate variability
hsCRP	High-sensitivity C-reactive protein
IMT	Intima media thickness
IVSed	Intraventricular septum end-diastolic
LA	Left atrium
LDL	Low density lipoprotein
LEPR	Leptin receptor
LF	Low frequency power (in heart rate variability measurements)

LFNU	Normalized unit of low frequency power (in heart rate variability measurements)
LnTP	Natural logarithm of total power (in heart rate variability measurements)
LVEDD	Left ventricle end-diastolic dimension
LVESD	Left ventricle end-systolic dimension
LVPWed	End-diastolic left ventricular posterior wall thickness
MRI	Magnetic resonance imaging
NS	Not significant
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PAI-I	Plasminogen activator inhibitor type 1 antigen
PVC	Premature ventricular contractions
rMSSD	Root mean square of successive difference (in heart rate variability measurements)
RR	Relative risk
RT	Radiotherapy
SDNN	Standard deviation of all NN-intervals (in heart rate variability measurements)
SDS	Standard deviation score
SMR	Standard mortality risk
SF	Shortening fraction
TBI	Total body irradiation
TP	Total power (in heart rate variability measurements)
t-PA	Tissue-type plasminogen activator antigen
TVI Et	Tissue Velocity Imaging of early diastole
vWF	Von Willebrand Factor
W/H-ratio	Ratio of waist circumference and hip circumference
WMS	Wall motion abnormality
WMSI	Wall motion score index

Dankwoord

Onderzoek doe je niet alleen. Dit proefschrift is het resultaat van een samenwerkingsverband tussen verschillende afdelingen binnen het Universitair Medisch Centrum Groningen (UMCG). Het is voor mij een vier jaar durende ontdekkingsreis geweest, waarin ik veel heb mogen leren van de ervaring van veel mensen met uiteenlopende achtergronden op zowel klinisch als wetenschappelijk gebied. Graag wil ik al deze mensen bedanken en enkele mensen in het bijzonder noemen.

In de allereerste plaats, heel veel dank aan de deelnemers aan dit onderzoek. Zonder jullie inzet en betrokkenheid was dit proefschrift er niet geweest. Ik heb grote bewondering voor de manier waarop velen van jullie omgaan met een leven na kanker en de soms ernstige late effecten van de vroegere behandeling, waardoor deze ziekte als een rode draad door jullie leven loopt, en blijft lopen. Het enthousiasme en de belangstelling voor ons onderzoek was bijzonder om te ervaren. Het was me een genoegen om jullie op de onderzoeksochtenden te begeleiden.

Tijdens mijn wetenschappelijke stage gedurende de studie geneeskunde werd ik gegrepen door het 'onderzoek doen'. Ik ben heel erg blij dat ik de kans heb gekregen dit klinische onderzoek binnen de afdelingen kinderoncologie en medische oncologie te doen. Ik wil mijn beide directe begeleiders, dr. A Postma en prof. dr. J.A. Gietema, bedanken voor hun begeleiding en hulp bij de uitvoering van dit onderzoek. Beste Liedeke, als co-promotor heb jij mij de liefde voor de kinderoncologie en in het bijzonder voor de late effecten na vroegere kinderkankerbehandeling overgebracht. Je was altijd bereid om te helpen en bood regelmatig een luisterend oor. Ik bewaar goede herinneringen aan de diverse congressen die we samen bezochten. Het was een plezier om met je samen te werken. Beste Jourik, onderzoek doen zit in je bloed. Je hebt mij aanvankelijk als co-promotor en in de laatste fase in de hoedanigheid van tweede promotor begeleid. Je leerde mij kritisch wetenschappelijk denken. Onze discussies hebben, denk ik, geleid tot mooie stukken. Dank voor de leerzame tijd.

Prof. dr. W.A. Kamps, beste Willem. Heel veel dank dat ik vier jaar geleden als onderzoeker mocht starten binnen de afdeling kinderoncologie. Ik wil je bedanken voor het bewaken van de grote lijnen en het meedenken aan de onderzoeksopzet en het uitwerken van de resultaten. Het was erg prettig om met vragen laagdrempelig bij je terecht te kunnen.
Prof. dr. E.G.E. de Vries, beste Liesbeth. Heel veel dank voor je betrokken en kritische beoordeling van onderzoeksopzet, -vragen en -resultaten. Het snelle tempo van het terugkrijgen van correcties op stukken is daarbij een erg prettige bijkomstigheid! Ik heb grote bewondering voor hoe één persoon zo'n gedetailleerde betrokkenheid kan hebben bij zoveel onderzoekers op een groot aantal verschillende onderzoeksgebieden.

I would like to thank prof. dr. K.C. Oeffinger for his participation in the review committee of this thesis and for his stimulating comments. Ook de overige leden van de beoordelingscommissie, prof. dr. H.N. Caron en prof. dr. D.J. van Veldhuizen, bedank ik voor hun bereidwilligheid mijn proefschrift te beoordelen.

De kern van onze onderzoeksgroep was klein, maar zeer fijn! Nynke Zwart, Ria Blaauwbroek en Wemke Tuinier zeg ik dank voor de gezellige tijd die we in de kamers G1.18 en G1.16 hebben mogen doorbrengen. Beste Nynke, dank voor al het werk dat je hebt verricht op ons project. De database en het laboratoriumwerk was bij jou in zorgvuldige en vertrouwde handen! Daarnaast kon ik altijd even mijn hart bij je luchten als een analyse weer eens tegenzat of toch maar weer helemaal anders moest. Beste Ria, ons promotietraject zijn we vrijwel gelijktijdig begonnen en we sluiten het nu ook gezamenlijk af. Het was altijd fijn met je samenwerken en ik heb veel van jouw nuchtere kijk op het leven geleerd. Fantastisch dat we nu op dezelfde dag promoveren! Beste Wemke, de eerste jaren van mijn promotietraject hebben we intensief samengewerkt en tussendoor was er regelmatig even tijd om onder het genot van koffie of thee en koekje bij te kletsen. Vervolgens altijd weer met frisse moed verder met onze beider analyses en schrijfactiviteiten. Ik heb bewondering voor je stap om nu de nurse-practioner opleiding te doen. Wellicht in de toekomst ook weer gecombineerd met onderzoek?

Dr. J.M. Vonk, beste Judith. Een onderzoek als dit is niets zonder een gedegen statistische onderbouwing. Ik heb door jou heel veel mogen leren over velerlei statistische toepassingen. We hebben de onderzoeksresultaten samen op veel verschillende manieren benaderd. Het was jou nooit te gek om het roer toch maar weer eens helemaal om te gooien. Met vragen kon ik bijna altijd direct bij je terecht. Veel dank voor al je hulp!

Bij de totstandkoming van de hoofdstukken uit dit proefschrift zijn diverse afdelingen uit het UMCG betrokken geweest. Allereerst, wil ik alle medewerkers van de polikliniek kinderoncologie bedanken voor hun medewerking aan het onderzoek. Gedurende de eerste drie jaren heb ik vele ochtenden achter de computer op de poli en in de infectiekamer mogen doorbrengen. Dank voor jullie interesse in het onderzoek en de gezellige uurtjes die ik bij jullie heb gehad!

Ook de echokamer van het Thoraxcentrum werd voor mij een vertrouwde plek binnen het UMCG. De echocardiografieën bij de deelnemers werden voorafgaand aan het normale echo-programma uitgevoerd en dit vooral dankzij de inzet van één van de echocardiografisten, Yoran Hummel. Vrijwel alle deelnemers (>400) werden door hem echocardiografisch in kaart gebracht. Beste Yoran, dank voor je bereidheid al deze

echo's te doen! Ik bewaar goede herinneringen aan het gezellige begin van iedere onderzoeksochtend. Als je er een keertje niet was, waren je collega's gelukkig altijd bereid om de echo te doen. Alle medewerkers van de echokamer wil ik bedanken voor de soepelheid waarmee deze omvangrijke onderzoekspopulatie echocardiografisch werd gescreend. Organisatorisch zeker geen gemakkelijke opgave.

Na afloop van de cardiologische screening besprak ik alle uitslagen door met dr. M.P. van den Berg. Beste Maarten, dank voor de introductie die je me in de cardiologie hebt gegeven. Je kritische benadering van zowel klinische als wetenschappelijke vraagstukken en het vasthouden van de hoofdlijn in het onderzoek heb ik als zeer prettig ervaren.

Dr. J Haaksma, specialist op het gebied van heart rate variability. Beste Jaap, dank voor je bereidheid de resultaten van de 24-uurs ECGs te beoordelen en in een database te zetten. Ook de overige medewerkers van de holterkamer: dank voor al jullie voorbereidende werkzaamheden!

Dr. M.Th.E. Bink-Boelkens, beste Margreet, ik kon altijd laagdrempelig bij je terecht om even over de uitkomsten van de cardiologische onderzoeken te spreken, in het bijzonder wat betreft de (24-uurs) ECGs. Dank voor je waardevolle bijdrage!

Een andere afdeling waar ik veel tijd heb mogen doorbrengen is het vaatlab, onderdeel van de interne geneeskunde. Dr. A. Smit was hier mijn directe aanspreekpunt. Beste Andries, dank voor de prettige samenwerking en voor de kritische en vlotte reacties op de manuscripten. Het team van het vaatlab wil ik bedanken voor het meten van de meer dan 400 deelnemers en het uitwerken van de resultaten. Het vasculaire onderzoek was het meest omvangrijke onderdeel van het onderzoek. Zowel uitvoering als uitwerking hebben veel tijd gekost. Beste Arie, Anne, Annet, Margreet, Marianne en Wietse, dank voor jullie medewerking en nauwkeurige meting en analyse van alle deelnemers!

Maaike Veldman, Gretha Beuker en Bianca Smit-Aeilkema wil ik bedanken voor de secretariële ondersteuning van dit proefschrift.

Alle overige mede-auteurs dank ik voor hun bijdrage aan één of meerdere hoofdstukken uit dit proefschrift: dr. H.M. Boezen, dr. W.V. Dolsma, dr. N.J. Elzenga en prof. dr. J. van de Meer.

Een klinisch onderzoek op zowel cardiologisch als vasculair gebied in een grote groep overlevenden van kinderkanker kost veel geld. Heel veel dank gaat dan ook uit naar

de Stichting "Quality of Life Gala 2003" die de realisering van dit project heeft mogelijk gemaakt.

Peter van der Sijde wil ik bedanken voor de lay-out van dit proefschrift.

Alle collega-onderzoekers van de afdeling kindergeneeskunde, lab kinderoncologie en lab medische oncologie wil ik bedanken voor de gezellige tijd die ik in Groningen heb gehad. In het bijzonder wil ik noemen, Eryn Liem en Carianne L'Abée. Lieve Eryn en Carianne, wij hebben elkaar leren kennen tijdens het assistentenweekend in Groningen en trokken als onderzoekers al gauw naar elkaar toe. Dat is uitgegroeid tot een vriendschap die verder reikt dan het delen van de pieken en dalen die bij het doen van onderzoek horen. Ik bewaar zeer goede herinneringen aan onze "buurvrouw-lunches" en hoop dat we die ondanks de nu wat grotere afstand toch nog regelmatig kunnen plannen. Ik ben vereerd dat jullie mijn paranimfen willen zijn op de grote dag!

De collega's uit het Wilhelmina Kinderziekenhuis te Utrecht wil ik bedanken voor de getoonde belangstelling in mijn onderzoek en de ruimte die mij werd gegeven om het proefschrift goed af te ronden.

Mijn familie, vrienden en vriendinnen wil ik bedanken voor de gezellige momenten naast het onderzoek doen. In het bijzonder wil ik noemen mijn vriendinnengroep uit de Achterhoek: Marloes, Willeke, Nanda en Hilly. Ondertussen wonen we verspreid over het gehele land, maar dat weerhoudt ons er niet van regelmatig af te spreken. Binnenkort hopelijk weer wat meer tijd!

Bij de Martinigemeente, en in het bijzonder de Noorderlichtkringen, heb ik naast mijn werk de mogelijkheid gehad voor persoonlijke verdieping. Ik wil André, Ellen, Geurt-Henk, Marike, Jaap, Janet, Jan, Anneke, Ingrid, Coos, Margriet, Judith en Roelof bedanken voor de goede tijd die ik hierin heb gehad.

Mijn familie wil ik bedanken voor hun betrokkenheid en steun bij de totstandkoming van dit proefschrift.

Lieve Harm-Jan, Tineke en Joline. Jullie houden mij als broer en zussen altijd weer met mijn beide beentjes op de grond. Dank voor de gezellige momenten die wij als 'sibs' vaak hebben.

Lieve papa en mama, dit proefschrift is voor jullie! Jullie hebben mij vanaf het begin gestimuleerd en gemotiveerd om mezelf te ontplooien en de weg te kiezen die ik graag zou willen. Het is een voorrecht jullie dochter te mogen zijn. Bedankt voor alles!

Mijn liefste Sjoerd, ik ben er trots op dat jij vandaag op deze dag naast mij staat. Vier jaar geleden besloot ik om onderzoek te gaan doen in het hoge noorden. Jij hebt mij daar altijd in aangemoedigd en gesteund, hoewel het betekende dat we elkaar dan alleen in de weekenden zouden zien. Dank voor je vertrouwen in mij en dat je mij telkens weer stimuleert om het beste uit mezelf te halen. Je bent mij zeer lief!

Inge

CURRICULUM VITAE

Cornelia Alberdina Johanna (Inge) Brouwer werd geboren op 4 augustus 1978 te Ellecom. Na het behalen van haar Atheneum diploma aan de scholengemeenschap Het Ulenhof College te Doetinchem in 1996, startte zij met de studie Geneeskunde aan de Radboud Universiteit te Nijmegen. In 2000 behaalde zij haar doctoraal examen en in 2002 haar artsexamen (cum laude). Van oktober 2002 tot juni 2004 werkte zij als arts-assistent kindergeneeskunde zowel in Ziekenhuis De Gelderse Vallei te Ede alsook in de Isala Klinieken te Zwolle. Op 1 juni 2004 werd zij aangesteld als arts-onderzoeker bij de vakgroep kinderoncologie van het Universitair Medisch Centrum Groningen. Aldaar deed zij een promotieonderzoek naar de cardiovasculaire late effecten van vroegere behandeling voor kinderkanker. Sinds juli 2008 is zij werkzaam als arts-assistent kindergeneeskunde in het Wilhelmina Kinderziekenhuis te Utrecht. In 2007 is ze getrouwd met Sjoerd Meulensteen.

LIST OF PUBLICATIONS

1. **C.A.J. Brouwer**, J.A. Gietema, M.P. van den Berg, M.T.E. Bink-Boelkens, N.J. Elzenga, J. Haaksma, W.A. Kamps, J.M. Vonk, E.G.E. de Vries, A. Postma. Progressive cardiotoxicity in survivors of a malignant bone tumour. Ann Oncol 2006;17(10):1586 – 1591.

2. **C.A.J. Brouwer**, J.A. Gietema, W.A. Kamps, E.G.E. de Vries, A. Postma. Changes in body composition after childhood cancer treatment: impact on future health status – a review. Crit Reviews Oncol Hematol 2007:63:32-46.

3. M. Wassenaar, **C.A.J. Brouwer**, J.M. Vonk, W.A. Kamps, A. Postma. Overgewicht na behandeling voor acute lymfatische leukemie bij kinderen. Tijdschrift voor kindergeneeskunde, 2007;4:133-138.

4. M.J. de Vos, **C.A.J. Brouwer**, J.M. Vonk, A. Postma. Body Mass Index (BMI) na behandeling voor solide tumoren op de kinderleeftijd. Tijdschrift voor Kindergeneeskunde, 2007;4:129-133.

5. **C.A.J. Brouwer**, J.A. Gietema, M.P. van den Berg, M.T. Bink-Boelkens, N.J. Elzenga, J. Haaksma, W.A. Kamps, J.M. Vonk, A. Postma. Low-dose anthracyclines in childhood ALL: no cardiac deterioration more than 20 years post-treatment. J Cancer Survivorship 2007;1(4):255-260.

6. **C.A.J. Brouwer**, A. Postma, J.M. Vonk, N. Zwart, M.P. van den Berg, M.T.E. Bink-Boelkens, W.V. Dolsma, A.J. Smit, E.G.E. de Vries, W.A. Kamps, J.A. Gietema. Subclinical systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. Submitted.

7. **C.A.J. Brouwer**, A. Postma, J.M. Vonk, N. Zwart, W.V. Dolsma, E.G.E. de Vries, W.A. Kamps, J.A. Gietema. Longitudinal evaluation of body mass index in association with earlier childhood cancer treatment. Submitted.

8. **C.A.J. Brouwer**, A. Postma, A.J. Smit, J.M. Vonk, A.M. van Roon, J. van de Meer, M.P. van den Berg, W.V. Dolsma, M.T.E. Bink-Boelkens, E.G.E. de Vries, W.A. Kamps, J.A. Gietema. Vascular damage in long-term childhood cancer survivors. Submitted.