Late effects after treatment for Hodgkin lymphoma

Laurien Daniëls

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contents

chapter I

Introduction and outline of the thesis

1.1 Background

Epidemiology

Hodgkin lymphoma (HL) is a relatively rare type of cancer. The incidence rate of HL over the past decade in the Netherlands was 2.3-2.7 per 100.000 persons per year (European standardized rate). The absolute annual incidence in the Netherlands in 2011 was 462, which accounts for approximately 2% of all newly diagnosed malignancies (1). Incidence of HL has remained stable. The majority of patients are younger than 35 years of age, which makes HL the third most common form of cancer in young adults. Response to treatment is generally good, leading to high disease-specific and overall survival rates. Currently, 5-year overall survival rates for the total group of HL patients are approximately 90%. Survival is highest in patients presenting with early stage disease, with 5-year overall survival rates of 90-98% (2, 3). Overall survival in patients presenting with more advanced disease ranges from 80-85% (4, 5).

HL is a lympho-proliferative disorder of B-lymphocytes, and mainly affects peripheral lymph nodes. HL is subdivided in several histological subtypes. Classical HL, consisting of nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes, accounts for approximately 95% of new HL cases. The remaining 5% is the nodular lymphocyte-predominant subtype. Little is known about the aetiology of HL. A possible relation with Epstein-Barr infection (EBV) has been suggested since EBV antigens have been detected in up to 30% of HL patients, especially in patients with the lymphocyte depleted subtype (6).

Staging

Staging in HL is important, both for predicting prognosis as well as for selection of optimal treatment. Staging occurs according to the Ann-Arbor classification system (Table 1.1), which reflects the number and spread of affected lymph node areas. It also takes into account systemic symptoms due to the lymphoma such as weight loss, night sweats or fever which are present in approximately 40% of HL patients (7, 8). Approximately two thirds of patients present with early stage (stage I-II) disease.

Table 1.1: Ann-Arbor staging system for HL (9)

Stage I	Involvement of a single lymph node region or extralymphatic region/organ (IE)
Stage II	Involvement of 2 or more lymph node regions or lymphatic structures on the same side of the diaphragm alone or extralymphatic regions on the same side of the diaphragm alone (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm with localized extralymphatic (IIIE) or splenic (IIIS) involvement or both (IIIES)
Stage IV	Involvement of one or more organs or tissues outside the lymphatic system, with or without involvement of nearby lymph nodes
	A: Without B symptoms
	B: Fever, night sweats, weight loss of $>$10% body weight over the last 6 months

Tailoring of therapy to prognostic risk factors such as stage of disease or presence of systemic symptoms has been investigated in the course of various clinical trials. The subdivision of early stage disease in a favourable and an unfavourable risk group, based on the presence of these prognostic factors had a significant impact on progression-free survival and overall survival (2). Although various HL study groups have defined different sets of prognostic risk factors (Table 1.2), all three of the cur-

Table 1.2: Risk factor definition in early stage (stage I-II) HL according to various study groups

GHSG	EORTC	NCCN
Large mediastinal mass (ratio $\geq$1/3)*	Large mediastinal mass (ratio $\geq$0.35)	Large mediastinal mass (ratio $\geq$1/3) Bulk $>$10 cm
	Age $\geq$50 years	
$\geq$1 extranodal lesion*		
ESR $\geq$50 (A) or $\geq$30 (B)	ESR $\geq$50 (A) or $\geq$30 (B)	ESR $\geq$50 (A) B-symptoms
$\geq$3 nodal areas (out of 11 GHSG areas)	$\geq$4 nodal areas (out of 5 supra-diaphragmatic EORTC areas)	$\geq$4 nodal regions (out of 17 Ann Arbor regions)

Patients are staged in the unfavourable risk group if at least one of the above listed factors is present. Within the GHSC system, patients with a large mediastinal mass as well as $\geq$1 extranodal lesion are considered as advanced stage and treated in accordance with stage III-IV HL (2). GHSG = German Hodgkin Study Group; EORTC = European Organisation for Research and Treatment of Cancer; NCCN = National Comprehensive Cancer Network.

rently defined classification systems are significantly related to outcome. Moreover, the classification into favourable and unfavourable risk groups has led to risk-adapted treatment strategies, in which patients presenting with unfavourable early stage disease receive more intensified treatment.

For patients presenting with advanced stage HL a different prognostic score is used for risk stratification. The most widely used prognostic index is the International Prognostic Score (IPS) which was developed based on outcome data of a large cohort of HL patients with advanced stage disease, treated in accordance with different HL study groups. The prognostic index contains seven clinical parameters, in which one point is assigned to each of the following risk factors:

- Age $\geq$45 years
- Male sex
- Stage IV disease
- Hemoglobin level $<$105 g/L
- White blood count $>15\times10^9$/L
- Lymphocyte count $<0.6\times10^9$/L or $<$8% of differential
- Albumin level $<$40 g/L

With increasing IPS scores, both progression-free survival and overall survival decrease (10).

Treatment

Over the past decades important improvements have been made in the treatment of HL. The earliest treatment of HL consisted of radiation therapy. In the 1950s orthovoltage (kilovoltage) radiation was used. Large radiotherapy fields were given but due to the physical properties of this type of radiation, penetrating only to a depth of 4-6 cm, outcomes were disappointing (11). After the introduction of megavolt irradiation with at first Cobalt machines followed by linear accelerators in the 1960s, deeper lymph node areas were much better reached. Moreover, with megavoltage radiation beams the dose distribution became more homogeneous. Consequently, with these improved radiotherapy techniques, outcomes improved significantly and survival rates of 50-60% were reached (12). In the absence of effective systemic treatment options, radiotherapy using large treatment volumes such as total nodal or subtotal nodal fields was the only curative treatment option for HL patients and remained standard of care until the 1980s. From the 1960s onwards, the majority of HL patients

have been treated within clinical studies designed to tailor treatment approaches to risk factors and improve treatment outcome.

For patients with early stage disease, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a first clinical study for the treatment of early stage HL in 1964. After surgical staging, including splenectomy and lymph node sampling, patients were randomized between radiation treatment alone, or radiation treatment followed by chemotherapy (weekly vinblastine during 2 years after completion of radiotherapy). This trial showed improved progression-free survival after combination therapy, but failed to show an improvement in overall survival, which was about 60% to 65% in both arms. Using the trial data a first effort was made in defining prognostic factors (13). In the next decades subsequent EORTC studies were conducted. Based on results of these studies it became clear that clinical staging of patients with HL was sufficient for determination of treatment, and surgical staging was abandoned, thus resulting in significant reduction of morbidity due to staging splenectomy. With the introduction of more potent multi-agent chemotherapy regimes in combination with radiotherapy, such as the MOPP regime (mechlorethamine, vincristine, procarbazine and prednisone) and MOPP-ABV (MOPP alternating with doxorubicin,bleomycin and vinblastine), clear improvements of both disease-free survival as well as overall survival were demonstrated. Survival now exceeded 85%, although event-free survival rates were lower. These highly effective chemotherapy regimes came, however, at the cost of serious side effects, such as infertility and (hematologic) secondary cancers (14). Radiotherapy therefore kept its prominent role in treatment, although an increasing number of studies showed that the extent of the radiotherapy fields could be reduced. Field sizes decreased from (sub)total nodal fields (all lymph node areas on both sides of the diaphragm) to mantle fields (all lymph node areas above the diaphragm) to involved fields (only treating the affected lymph node areas). It became increasingly evident that favourable outcome results were maintained with the combined modality treatment approach using these new chemotherapy regimes followed by involved-field radiotherapy with a lower total radiation dose, and this approach became the new standard of care (3).

However, in due time it became clear that not only treatment with chemotherapy but also treatment with radiotherapy led to an increased risk of potentially serious long-term complications. These complications are often not seen until 10-15 years after completing radiation treatment, and risks do not subside over time (15). The first effort to omit radiotherapy completely from the treatment of patients with early stage HL with a favourable prognosis was made in the EORTC H9 trial. Unfortunately, a 25% reduced event-free survival was seen in patients who did not receive radiotherapy. It has been suggested that this might, in part, be due to the less toxic,

but potentially less effective EBVP (epirubicin, bleomycin, vinblastin and prednisone) chemotherapy regime used in this study.

The recent H10 study investigated the possibility of treatment adaption in early stage HL, based on chemotherapy response measured by interim fluordeoxyglucose positron emission tomography scan (FDG-PET scan). Patients with favourable prognostic features who had a negative FDG-PET after two courses of ABVD chemotherapy were randomized between involved node radiotherapy or no further treatment. This arm of the study was closed prematurely after an interim analysis showed an increase in recurrent disease in patients who did not receive radiation therapy (16). Currently, there is no evidence that radiotherapy can be fully omitted from treatment of HL patients with early stage disease without compromising at least progression-free survival (17, 18).

The role of radiotherapy in the treatment of advanced stage HL has been limited (19). Key part of the treatment for advanced stage disease has been systemic treatment. Over the past decades increasingly effective chemotherapy agents have been tested. In a meta-analysis the role of additional radiation treatment was explored. An increase in tumor control was demonstrated, however without an increase in overall survival (20). The EORTC H3/4 trial evaluated the role of radiotherapy after systemic treatment, and showed no benefit of radiotherapy in patients in complete response after chemotherapy. However, patients in partial response after systemic treatment did benefit from involved field radiotherapy in terms of increased progression-free and overall survival (21).

1.2 Late treatment effects

Cure of HL may come at a cost. In the past decades it has become increasingly evident that both radiotherapy and chemotherapy can cause numerous long-term adverse effects. While the risk of of mortality due to HL abates with time, overall (all-cause) survival of HL survivors continues to decrease at a higher rate compared to an age matched norm population. This is due to morbidity and mortality from late treatment sequelae (Figure 1.1)(22, 23). Radiation-induced late treatment effects progressively increase from 10 to 15 years after initial treatment. Epidemiological studies have shown that even after 30 years of follow-up the relative risks (RR) of developing late treatment complications do not decline (23).

Numerous late treatment sequelae have been described in epidemiological stud-

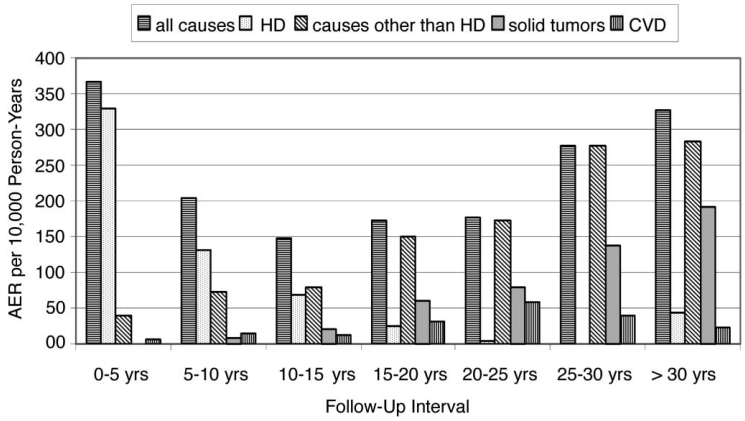

Figure 1.1: Absolute excess mortality from various disease categories over time, from a cohort of 1261 HL survivors. Mortality from HD decrease, while mortality due to solitary tumors and cardiovascular disease increase over time (23). HD = Hodgkin disease, CVD = cardiovascular disease AER = absolute excess risk.

ies after treatment with chemotherapy, radiotherapy or a combination of these modalities for HL (Figure 1.2).

Secondary tumors

One of the most serious long-term complications of treatment for HL is the induction of secondary cancers. In the first ten years after treatment patients are mainly at risk of developing secondary haematological cancers due to exposure to chemotherapy. An increased risk of acute leukaemia and myelodysplastic syndrome was found in patients treated with various chemotherapy regimes, especially after receiving alkylating agents (25). The relative risk of secondary Non-Hodgkin lymphomas is also significantly increased, both in patients treated with chemotherapy as well as after treatment with radiotherapy (RR 17, 95% CI 10-27)(26). From approximately 10 to 15 years after treatment the risk of developing radiation-induced solid tumors increases. Solid tumors account for the majority of second cancers in HL survivors. The most common second malignancy is breast cancer in female HL survivors treated with thoracic (mediastinal and/or axillary) radiotherapy. Compared to the general population, these patients have a 5-fold increased risk of breast cancer (27). Risks are

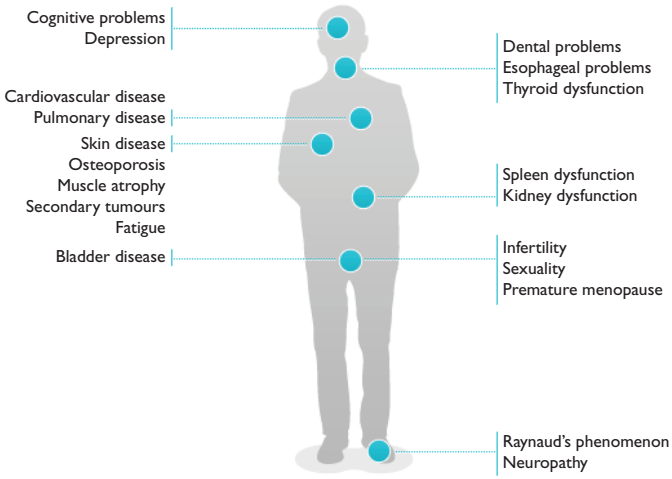

Figure 1.2: An overview of possible late treatment sequelae after treatment with chemotherapy, radiotherapy or a combination of these modalities (24).

especially increased in patients treated before the age of 30, and especially before the age of 20 (Figure 1.3).

The volume of breast tissue covered by the radiation treatment fields (mantle fields including mediastinal and axillary fields vs. only superior mediastinal fields) also has a significant impact on the risk of developing breast cancer. Decreasing radiation volumes lead to a reduction in risk of breast cancer (27). It has been demonstrated that survival is higher when breast cancer in female HL survivors is detected in an early stage. For this reason, current follow-up guidelines for HL recommend screening of female HL survivors at risk for developing radiation induced breast cancer.

HL survivors are also at risk of developing several other types of solid tumors. As with breast cancer, risks depends on age at treatment of HL, time since treatment, location of radiation treatment fields and radiation dose. Risks of developing lung cancer (especially in smokers), thyroid cancer, cancers of the gastro-intestinal tract after abdominal radiotherapy, and of bone and soft tissue malignancies are all increased after treatment with radiotherapy (Table 1.3). However, since the absolute risk of developing any of these types of cancer is low, at present screening is not recommended.

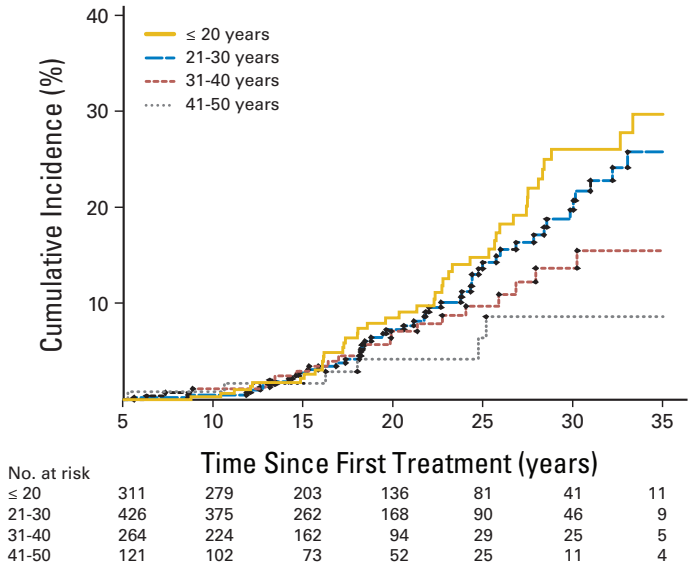

Figure 1.3: Absolute cumulative incidence of breast cancer in women treated with radiotherapy for HL. Risk of breast cancer is highest in patients treated at a younger age. Data are collected from a cohort of 1122 Dutch HL survivors all treated with radiotherapy between 1965-1995 (27).

Table 1.3: Standardized incidence ratios of various types of secondary solid tumors

Type of cancer	Standardized Incidence Ratio	References
Breast cancer	1.3–11.6	(22, 28-32)
Lung cancer	1.8–6.7	(28–30, 32)
Thyroid cancer	3.1–8.6	(22, 28, 30, 31, 33)
Stomach cancer	1.6–9.5	(28, 30, 31, 33)
Oesofageal cancer	1.9–4.2	(28, 30, 31, 33)
Colon cancer	1.6–4.3	(28, 30, 31, 33)

Standardized incidence ratio reflects the proportion of observed secondary tumors in comparison to the number of expected tumors in the general population.

Cardiovascular disease

The most common nonmalignant long-term complication in HL survivors is development of cardiac disease. Late cardiac complications are observed both in patients treated with chemotherapy, and /or radiotherapy to the mediastinum. Since the majority of HL patients presents with involved mediastinal lymph nodes this area is often included in the radiation treatment fields.

A wide spectrum of cardiovascular diseases may occur after mediastinal radiotherapy. Historically, one of the most common radiation induced complications was acute radiation pericarditis, due to increased vascular permeability leading to fluid extravasation (34). In 10-20% of patients this progresses into fibrotic thickening of the pericardium, leading to chronic constrictive pericarditis (35). The introduction of linear accelerators has led to a decrease of the radiotherapy doses to the pericardium, and with the reduction of treatment fields, the incidence of pericarditis had decreased significantly from 20% to 2,5% (36).

In screening studies, valvular disease such as thickening, retraction and calcification of the valves, is observed in up to 40-60% of patients treated with mediastinal radiotherapy (37, 38). Valvular calcifications are most often seen at the aortic and mitral valves. Valvular disease can lead to impaired functioning of the cardiac valves. However, most patients remain asymptomatic up to the point where they present with severe symptoms of heart failure (34).

Conduction disorders have also been described after mediastinal radiotherapy, due to either fibrosis of tissue adjacent to the conduction system or due to direct damage (39). Abnormalities most often concern right bundle branch blocks (40), and first-degree atrioventricular blocks (34). Patients most commonly report episodes of syncope.

Mediastinal radiotherapy fields often encompass the origin and proximal part of the coronary arteries. Over time, this can lead to atherosclerotic coronary artery disease. The pathogenesis of this process is likely to involve a variety of mechanisms. Radiation damage to the vasculature of the heart can lead to an inflammatory response (36). This response leads to proliferation of the intima, the inner layer of the vessel wall containing endothelial cells, and deposition of collagen. The subsequent thickening of the endothelium can lead to dysfunction, which is believed to result from a combination of impaired endothelial function, upregulation of growth factors and eventually fibrosis (41). Progressive fibrosis and replacement of damaged cells with myofibrablasts along with platelet depositions then causes coronary plaque formation and narrowing of the coronary artery vessel lumen resulting in coronary artery stenosis (36).

Coronary artery stenosis is a relatively frequent late complication in HL patients

who have been treated with mediastinal radiotherapy. Severe coronary artery stenosis can limit the blood flow to the myocardium and thus cause myocardial infarction, the most common cause of cardiovascular death. The risk of myocardial infarction in HL survivors has been evaluated in several epidemiological studies, and was compared to an age- and sex matched normative population. Swerdlow *et al.* demonstrated a hazard rate (HR) of 3.2 for mortality due to myocardial infarction in a cohort of 7033 HL survivors treated with mediastinal irradiation after a median follow-up of 11.2 years (42). In the Netherlands a comparable result was found by Aleman *et al.* among 1474 HL survivors (43). The standardized incidence rate for myocardial infarction, a measure that reflects the ratio of observed events as compared to the number of events within a normal population, was 3.7; which resulted in 35.7 extra patients with myocardial infarction per 10.000 person years. Despite these established increased risks of coronary artery disease and risk of myocardial infarction, the role of screening for cardiac abnormalities remains unclear.

Other adverse physical late effects

Apart from second malignancies and cardiovascular disease, survivors from HL are confronted with a variety of other adverse physical late treatment effects. Radiation of the thyroid region can lead to impaired function of thyroid gland. Most often, this involves a subclinical hypothyroidism, a decrease in thyroid function which is compensated by elevated levels of Thyroid Stimulating Hormone. Impaired thyroid function, if left untreated, can lead to a range of unexplained symptoms such as loss of hair, dry skin, muscle aches but also feelings of loss of energy or depression. Subclinical thyroid dysfunction is found in 5-60% of HL patients receiving radiotherapy of the neck (44-46), and can be easily treated with oral thyroid hormone supplements. Patients should be routinely screened for (subclinical) thyroid dysfunction. Radiation of the shoulder and neck region in time can cause atrophy of muscles and fibrosis of connective tissues. Symptoms range from stiffness and pain in the head and neck region to the "dropped head syndrome" which is characterized by severe weakness of the cervical muscles resulting in difficulties with keeping the head lifted and can even cause complaints of severe headaches. These symptoms are most often seen after treatment with mantle field irradiation, which encompasses a large proportion of the neck- and shoulder musculature (47). Prevalence increases over time, and ranges between studies from 20% to 70% (47, 48). Some patients benefit from physiotherapy treatment aimed at increasing muscle strength, or wearing a neck collar (47, 49).

With older treatment strategies, it was custom to remove the spleen for the purpose of disease staging, or to irradiate the spleen to a high dose. Without (a func-

tional) spleen the body is unable to respond adequately to certain types of bacterial infections, which can result in the occurrence of rapid fatal infections. Preventative strategies using pneumococcal and influenza vaccination schedules and prompt antibiotics if needed should routinely be employed.

Fatigue and health-related quality of life

Apart from the risk of long-term adverse effects discussed above, many HL survivors also report to suffer from long-term psychosomatic and psychosocial problems. Since the 1990s there has been increasing interest in these aspects of late treatment sequelae, and in the burden associated with being a cancer survivor. Patient reported outcome measures such as health-related quality of life studies are reported with increasing frequency. These studies have highlighted the specific needs and difficulties of the growing population of cancer survivors (50). HL patients are often treated and cured at a young age, which means that late side effects of treatment influence a large part of their adult life.

In daily practice, fatigue is one of the most frequently reported symptoms accompanying cancer, and often persists over time (51). It often has a strong negative impact on health-related quality of life, and is reported to be of more impact than pain or other symptoms (52). Several cross-sectional studies have evaluated the prevalence of fatigue in HL patients. However, fatigue is also a frequently reported problem in the general population. Only a few studies have compared prevalence of fatigue in HL survivors to the general population, but all report a significant increase in fatigue in HL survivors (53, 54). Also, the reported level of fatigue is significantly increased compared to age- and sex matched control populations (54, 55).

Several studies have explored patient and treatment related factors influencing levels of fatigue, but often provide conflicting results (54, 56-58). It therefore remains difficult to indicate which factors have the largest impact on the occurrence and persistence of fatigue. Better understanding of factors influencing fatigue could help in developing specific interventions at prevention or treatment of adverse psychosomatic and psychosocial symptoms, or to improve information provision to cancer survivors. It would also provide options for the training of clinicians in the care for this specific population.

Outpatient late effects screening clinics ('BETER')

In view of the late side effects of treatment in HL, a nationwide network of specialized long-term HL follow-up clinics has been started in the Netherlands, aimed at prevention, early detection and treatment of late treatment sequelae and to ensure optimal patient education and support. In the seven participating hospitals approximately 2800 HL survivors treated between 1965-1995 who should be considered for surveillance at this dedicated outpatient clinic have been identified. A close collaboration of radiation-oncologists, haematologists and epidemiologists will promote the development of evidence-based follow-up guidelines and enhance possibilities for research strategies for these patients. For HL survivors, the website www.beternahodgkin.nl was developed, which offers detailed information on treatment and possible late treatment sequelae.

1.3 Aims and outline of this thesis

The studies described in this thesis aimed to address and investigate several late effects of radiation therapy in HL survivors that have not yet been adequately studied. In HL survivors, the risk of several secondary cancers such as breast cancer have been well documented. However, little is known of the risk of secondary skin cancers due to radiation treatment. In **chapter 2** we report on the risk of developing skin cancers after treatment for HL in a large patient cohort treated at Leiden University Medical Center, and relate findings to an age- and sex matched norm population. Furthermore, epidemiological studies have established an increased risk of coronary artery disease (CAD) in HL survivors, resulting in significantly increased risks of myocardial infarction. The role of screening for CAD remains unclear. In **chapter 3** we report the results of a phase II screening study among HL survivors who are considered to have a high risk of radiation induced heart disease based on initial treatment parameters. We also evaluated quality of information provision on late side effects and impact on health-related quality of life of cardiac screening in this study population, which is reported in **chapter 4**.

Health-related quality of life can be affected by late treatment sequelae. Among the most frequently reported symptoms interfering with daily activities are fatigue and loss of energy and vitality. Several studies have evaluated the prevalence of fatigue and associations between patient and treatment related factors and severity of fatigue. In **chapter 5** we present an overview of current data on fatigue and factors

influencing levels of fatigue. Many studies have focused on the association between patient- and treatment characteristics and fatigue. Fatigue is also a frequent symptom of depression. Little is known, however, of the relation between fatigue and depression or anxiety in HL survivors. **Chapter 6** describes results from a cross-sectional survey among HL survivors assessing the association of fatigue with depression, anxiety and comorbidity, and comparison of the results with those from an age- and sex matched normative population.

In **Chapter 7** the main findings of the studies in this thesis are summarized and discussed, and the implications of these and other studies for long-term follow-up and screening of HL survivors are put into clinical perspective. Specific recommendations for future studies and for long-time care, counseling and support of HL survivors are made, with the aim of improving their event-free survival and quality of life.

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chapter 2

Long-term risk of secondary skin cancers after radiation therapy for Hodgkin lymphoma

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Abstract

Purpose
Survivors of Hodgkin's lymphoma (HL) are at risk of secondary tumors. We investigated the risk of secondary skin cancers after radiotherapy compared to treatment without radiation and to an age-matched population.

Methods
We conducted a retrospective cohort study of 889 HL patients treated between 1965 and 2005. Data on secondary skin cancers and treatment fields were retrieved. Incidence rates were compared to observed rates in the Dutch population.

Results
318 skin cancers were diagnosed in 86 patients, showing significantly higher risks of skin cancers, the majority being BCC. The standardized incidence ratio (SIR) of BCC in HL survivors was significantly increased (SIR 5.2, 95% CI 4.0–6.6), especially in those aged <35 years at diagnosis (SIR 8.0, 95% CI 5.8–10.7). SIR increased with longer follow-up to 15.9 (95% CI 9.1–25.9) after 35 years, with 626 excess cases per 10.000 patients per year. Most (57%) skin cancers developed within the radiation fields, with significantly increased risk in patients treated with radiotherapy compared to chemotherapy alone (p=0.047, HR 2.75, 95% CI 1.01–7.45).

Conclusions
Radiotherapy for HL is associated with a strongly increased long-term risk of secondary skin cancers, both compared to the general population and to treatment with chemotherapy alone.

Introduction

With the introduction of effective chemotherapy agents and the development of modern radiotherapy techniques, the overall and relapse-free survival rates for patients with Hodgkin's lymphoma (HL) have improved dramatically. With increasing numbers of long-term survivors of HL, the evaluation of late treatment sequelae has become of major importance. The increased long-term risk of secondary cancers due to radiotherapy has been established in numerous studies (1-6). The excess risks of several types of secondary tumors in or near the previous radiation fields have been found to be associated with radiation dose, time since radiation and age at initial treatment (7, 8). Patients treated at a young age, those treated to the mediastinal and axillary lymph nodes with relatively high doses of radiotherapy, and especially those treated with extended (subtotal nodal) radiation fields are at risk for developing secondary cancers (7). Increased rates of secondary solid tumors, such as breast cancer, are usually seen from 10 to 15 years after exposure to irradiation onward (9-12).

Epidemiological studies have established previous radiation therapy as a risk factor for the development of skin cancers, mainly basal cell carcinoma (BCC)(13). These studies have predominantly described large cohorts of children, treated at a very early age with moderate radiation doses. Shore *et al.* reported a relative risk of 3.6 for the development of skin cancer when comparing a cohort of 2.224 children irradiated with a median dose of 4.8 Gy to the scalp for tinea capitis to a control group of 1.380 children merely treated with topical medications (14).

Several case-control studies have found similar odds ratios (OR)(15). Watt *et al.* compared 199 childhood survivors of cancer developing BCC during follow-up to 597 age-matched childhood survivors without BCC and found an increased risk for BCC in patients treated with radiotherapy. Risk of developing BCC increased with higher radiation treatment dose(16).

Few studies in HL survivors have focused on the risk of developing secondary skin cancers: Swerdlow *et al.* reported a significantly increased standardized incidence ratio (SIR) of non-melanoma skin cancer of 3.9 in 1039 patients treated for HL(17). Increased risks of melanoma (SIR 8.0) have been described in Australian HL survivors (18).

The present study was undertaken to investigate the long-term risk of developing secondary skin cancer after radiation therapy (RT) in a large cohort of HL survivors compared to those treated without RT and to the general Dutch population, and to relate the location of skin cancers to the radiation fields.

Methods

Patients and treatment

Leiden University Medical Center (LUMC) is a regional center of expertise for diagnosis and treatment of HL patients. Data on all treated oncology patients are collected in a central database. We conducted a retrospective cohort study of all HL patients treated between 1965 and 2005 to establish the incidence of skin cancers in HL patients treated with radiation therapy alone or with combined modality treatment (radiotherapy and chemotherapy, either as primary treatment or at relapse) in comparison to those treated with chemotherapy alone. The timeframe 1965-2005 was chosen to assess long-term risks and have a sufficient time interval since treatment to analyze radiation-induced tumors, which usually develop from 10 to15 years after treatment onwards.

From the LUMC cancer registry system (OncDoc) we collected information on age at diagnosis, gender, stage of HL, treatment modality, treatment phase (primary treatment or for recurrent disease), survival and date of death. OncDoc performs an independent and active follow-up by annually updating their database through the Dutch Municipal Population Registries, supplemented with data from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA(19)), patient files and contact with family doctors in case of patients lost to follow-up or with unknown cause of death. This resulted in this study in a nearly complete (95%) follow-up registration up to January 19th 2011.

For information on the occurrence of skin cancers in HL patients we consulted PALGA(19). This is a nationwide organization with a central archive for pathology reports from all pathology laboratories in the Netherlands, which was founded in 1971, and had increasing participation in subsequent years. Since 1989 the registration has nationwide coverage. After the PALGA Internal Review Board approval, a search of subsequent pathology diagnoses in our HL patient cohort was conducted to identify those diagnosed with skin cancers. The search was performed by matching patients on date of birth, sex, and last name.

Skin cancer was defined as a histological diagnosis of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma of the skin. Date(s) of diagnosis and site(s) of first and any subsequent occurrence of skin cancer were established from the PALGA reports. Data were extracted on January 19th 2011. For patients who had developed skin cancers, detailed information on HL treatment and location and dose of the radiation treatment fields was collected in order to examine the type and location of the secondary skin cancers in relation to the radiation fields and doses. Follow-up ended at January 19th 2011.

Incidence rates of skin cancers, including BCC which was the predominant form of skin cancer in our cohort, were compared to observed incidence rates in the Netherlands obtained from the population-based Cancer Registry of the Comprehensive Cancer Center South (for BCC) and the Netherlands Cancer Registry (for SCC and melanoma)(20, 21).

Statistical analysis

All statistical analyses were performed using SPSS statistical software for windows version 17 (SPSS inc., Chicago, IL, USA) and STATA statistical software for windows version 11 (StataCorp LP, College Station, Texas, USA). Differences in characteristics of patients treated with chemotherapy alone or with radiotherapy were evaluated using chi-square (categorical variables) and analysis of variance (numerical variables). Correlations of skin cancer locations to the radiation fields were done in a descriptive manner.

The number of first skin cancers (BCC, SCC or melanoma) in the cohort was compared with the expected number in the Dutch population, based on age, sex- and calendar period- specific incidence rates for the period from 1989 through 2005. Time at risk started at date of HL diagnosis. Because the registration of the occurrence of skin cancers by PALGA was not complete until 1988, we left-censored within the timeframe 1965–1988. Therefore, patients at risk between 1965 and 1988 did not contribute person-time to our analysis during this timeframe. Time at risk ended at an event of a first skin cancer occurrence, last date of follow-up, death or other loss to follow-up, whichever occurred first. The SIR, defined as the observed (O) divided by the expected (E) numbers of BCC, SCC and melanoma were determined and corresponding 95% confidence intervals were calculated based on the Poisson distribution of observed numbers. Absolute excess risks (AER) were calculated as the observed incidence of skin cancers minus the number expected, divided by the number of person-years at risk and multiplied by 10,000.

Cumulative incidence of skin cancer in HL survivors treated with and without radiotherapy was estimated accounting for death as competing risk (22). To determine the influence of the possible incomplete event registration between 1965 and 1988, results were calculated both without and with left censoring. Hazard ratios and 95% confidence intervals (CI) were calculated by competing risk regression, both unadjusted and corrected for age, sex, year of diagnosis, and treatment period. A two-sided p-value <0.05 was considered statistically significant.

Table 2.1: Characteristics of HL survivors cohort

	Total number of patients	%	RT	%	No RT	%	P-value
Total	889		750		139		
Median age at diagnosis (range)	30 (5-84)		30 (5-84)		34 (10-78)		p=0.69
Treatment*							
Radiotherapy	251	28					
Chemotherapy	139	16					
Chemo- and radiotherapy	499	56					
Sex							p=0.13
Male	505	57	418	56	87	62	
Female	384	43	332	44	52	38	
Year of diagnosis							p=0.60
1965-1975	216	24	171	23	45	33	
1976-1985	233	26	194	26	39	28	
1986-1995	231	26	200	26	31	22	
1996-2005	209	24	185	25	24	17	
Stage (Ann-Arbor)							$p<0.001$
I	209	23	204	27	5	4	
II	456	51	437	58	19	14	
III	103	12	44	6	59	42	
IV	104	12	51	7	53	38	
Unknown	17	2	14	2	3	2	
Relapse							p=0.86
Yes	187	21	157	20	30	22	
No	702	79	593	80	109	78	

* including treatment for relapse. RT = radiotherapy.

Results

Between January 1st 1965 and December 31st 2005 a total of 889 patients were treated for HL at LUMC. Median age at diagnosis was 30 years (range 5-84 years). Of these, 139 patients (16%) were treated with chemotherapy alone, 251 (28%) with radiotherapy alone and 499 (56%) with a combination of these two modalities, either as primary treatment or as treatment for relapse of disease. Table 2.1 gives an overview of patient characteristics of the HL cohort.

Table 2.2: Characteristics of patients with skin cancer

Treatment	Number	%
Radiotherapy	39	45
Chemotherapy and radiotherapy	43	50
Chemotherapy only	4	5
Mean dose of radiotherapy (Gy, range)	35 (24-45)	
Chemotherapy regimes used	Number	%
MOPP	17	36
MOPP-ABV	12	26
ABVD	7	15
Other	8	17
Unknown	3	6
Age and time interval	Years	Range
Median interval of HL treatment to skin cancer	18	1-37
Median age at diagnosis of first skin cancer	52	25-80
Number of skin cancers	Number	%
Total number of skin cancers	318	
Mean number of skin cancers per patient (range)	4 (1-44)	
1	44	52
2 -5	28	33
6-10	8	8
≥11	6	7
Histology of skin cancers	Number	%
Total	318	100
Basal cell carcinoma	294	93
Squamous cell carcinoma	14	4
Melanoma of the skin	10	3
Relation of skin cancer to radiation field (per skin cancer)	Number	%
No radiotherapy	10	
Radiotherapy	308	
Within radiation field	175	57
Outside radiation field	87	28
* *Head and neck*	**65*	
* *Trunk*	**12*	
* *Limbs*	**10*	
Unknown	46	15
Relation of skin cancer to radiation field (per patient)	Number	%
No radiotherapy	4	
Radiotherapy	82	100
Within radiation field	23	28
Outside radiation field	23	28
* *Head and neck*	**13*	
* *Trunk*	**4*	
* *Limbs*	**6*	
Unknown	21	26

* Subgroup of skin cancers developing outside radiation fields.

Table 2.3: Standardized incidence ratios of first skin cancer in HL survivors

Diagnosis	Observed	Expected	SIR	95 % CI	AER*
Skin, melanoma	6	2.3	2.6	0.9-5.6	3.6
Skin, squamous cell	10	1.9	5.0	2.4-9.2	7.9
BCC of skin, head & neck	17	8.0	2.1	1.2-3.4	8.8
BCC of skin, trunk	36	3.0	11.7	8.2-16.2	32.4
BCC of skin, limbs	3	1.7	1.7	0.3-5.0	1.2
BCC of skin, other & NOS	11	.05	185.6	92.7-332.1	10.8
BCC of skin, total	67	12.9	5.2	4.0-6.6	53.3

Abbreviations: BCC = basal cell carcinoma; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk; NOS = not otherwise specified.

* per 10.000 persons per year.

Over the time period considered, 86 patients developed a total number of 318 skin cancers at a median interval of 18 years (range 1-37 years). Mean number of subsequent skin cancers was 4 per patient (range 1-44). Among the 318 skin cancers, 294 (93%) were BCC, 14 (4%) were SCC and 10 (3%) melanomas of the skin (Table 2.2).

When comparing the incidence rates of BCC, SCC and melanoma in our patient cohort to the incidence rates found in the Dutch population, the overall SIR for development of BCC was 5.2 (95% CI 4.0-6.6, Table 2.3), resulting in 53 excess cases of BCC per 10,000 persons per year. SIRs for SCC and melanoma were 5.0 (95% CI 2.4-9.2) and 2.3 (95% CI 0.9-5.6), respectively. When comparing incidence rates of BCC at specific anatomic locations, the rates were especially increased in the chest and trunk area (SIR 11.7, 95% CI 8.2-16.2), which is the predominant location of radiotherapy fields since most patients received either mantle fields or mediastinal involved field radiotherapy.

The SIR for BCC was clearly higher in patients who had received radiotherapy as part of their treatment, than in those who received chemotherapy alone (Table 2.4). SIRs after radiotherapy were 7.9 (95% CI 5.5-11.2) for radiotherapy alone and 4.1 (95% CI 2.8-6.0) for combined modality treatment (CMT), compared to 2.6 (95% CI 0.7-6.6) after chemotherapy (CT) alone.

The risks of developing secondary BCC were especially increased in patients treated for HL before the age of 35 years (SIR 8.0 95% CI 5.8-10.7, Table 2.4) and those treated between 35 and 65 years of age (SIR 3.1, 95% CI 1.9-4.9) and close to unity in patients treated after the age of 65. SIRs increased with longer follow-up; after 35 years the SIR was 15.9 (95% CI 9.1-25.9), with 626 excess cases per 10.000 patients per year. There were no significant differences in incidence between men and women.

Table 2.4: Risk of first BCC compared to the general Dutch population

Sex	PY	O	SIR	95% CI	AER*
Male	5415	39	5.7	4.0-7.7	59.4
Female	4740	28	4.6	3.0-6.7	46.2
Age at diagnosis	PY	O	SIR	95% CI	AER*
<35	7341	46	8.0	5.8-10.7	54.9
35-65	2653	20	3.1	1.9-4.9	51.7
>65	161	1	1.1	0-6.2	6.8
Treatment	PY	O	SIR	95% CI	AER*
CT	3073	4	2.6	0.7-6.6	22.5
RT	1086	33	7.9	5.5-11.2	93.9
RT + CT	5996	30	4.1	2.8-6.0	38.0
Treatment period	PY	O	SIR	95% CI	AER*
1965–1975	1747	25	7.1	4.5-10.5	122.9
1976–1985	2749	13	3.5	1.9-6.1	33.9
1986–1995	3726	20	5.1	3.2-7.9	43.3
1996–2005	1932	9	4.8	2.2-9.1	36.9
Follow-up interval	PY	O	SIR	95% CI	AER*
0–1 yrs	395	0	0	-	-
1–5 yrs	1676	2	1.8	0.2-6.3	5.1
5–10 yrs	2082	5	3.0	0.9-7.0	16.0
10–15 yrs	1829	4	2.1	0.6-5.5	11.7
15–20 yrs	1572	6	2.8	1.0-6.2	24.7
20–25 yrs	1215	14	6.7	3.7-11.3	98.1
25–29 yrs	745	10	6.3	3.0-11.7	113.0
30–34 yrs	400	10	8.0	3.8-14.7	218.7
>35 yrs	239	16	15.9	9.1-25.9	626.4

Abbreviations: PY = person years; O = observed; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk.

* per 10.000 persons per year.

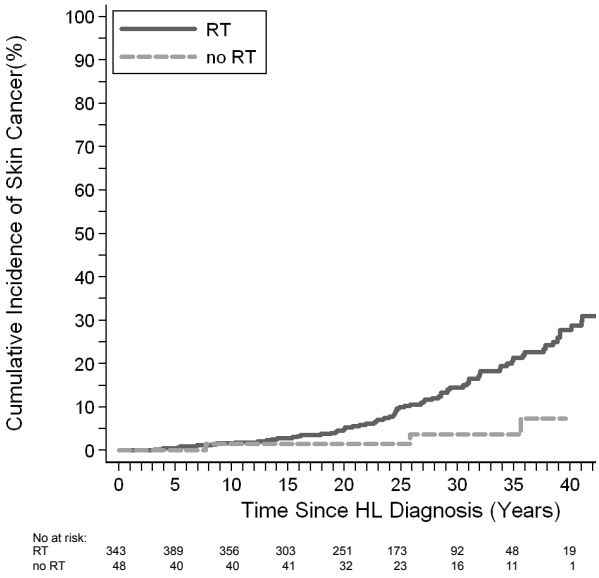

Figure 2.1: Cumulative incidence of developing a first skin cancer in the HL survivor cohort after treatment which included radiotherapy (RT; either RT alone or combined modality treatment) vs. treatment with chemotherapy alone (No RT).

The risk of development of skin cancer was significantly increased in patients who had received RT as (part of) their treatment, when compared to those treated with chemotherapy alone (unadjusted p=0·030, HR 2.95, 95% CI 1.11-7.86, adjusted p=0.047, HR 2.75, 95% CI 1.01-7.45). Cumulative incidences of developing skin cancer were 1.5%, 5% and 15% at 10, 20 and 30 years after treatment with radiotherapy, respectively, compared to 1.5%, 1.5% and 4%, respectively, for those treated with chemotherapy alone (see Figure 2.1).

The correlation of each separate skin cancer to the radiation fields is described in Table 2.2. The majority of skin cancers developed within radiation fields (57%). For those developing outside treatment fields an assessment was made of the distance to the radiation field borders, given that skin cancers in close proximity to the radiation treatment fields could have developed either due to scatter irradiation near the field, or within the radiation penumbra. Of the 87 skin cancers that had developed out of field, 12 (14%) were located close to the radiation field border. For 15% of all

skin tumors no relation to the radiation fields could be established, due to missing descriptions of precise anatomic locations in PALGA pathology reports.

Of the 10 skin cancers developing within five years after initial treatment for HL, 1 developed within the radiation treatment fields (10%). In contrast, of the 210 skin cancers developing more than 20 years after treatment, 127 (60%) developed within the radiation field.

Among patients who developed secondary skin cancers, 28% developed tumors only within radiation fields, 26% developed skin cancers both within and out of the fields, and 28% only outside the radiation fields (18% unknown, Table 2.2). These numbers changed only slightly when limiting the analysis to BCC (31% within fields, 31% both within and out of field). Among the patients with only one BCC, 54% of the tumors developed within field.

Most skin cancers were treated with simple excision, but specific information on subsequent follow up was not available. None of the patients died from the results of basal cell carcinoma, squamous cell carcinoma or melanoma of the skin.

Discussion

This study investigated the long-term risk of developing secondary skin cancers in a large cohort of HL survivors. We found significantly increased risks of subsequent skin cancers in HL patients treated with radiation therapy as compared to those treated with chemotherapy alone. The predominant form of skin cancer observed was BCC. Risks of developing BCC were substantially increased when compared to the general Dutch population and strongly increased with longer follow-up.

To our knowledge, this is one of the largest cohort studies presenting risks of skin cancer in patients treated with moderately to high doses of radiotherapy, with long-term and nearly complete follow-up. We calculated cumulative incidence rates of developing skin cancer with death as competing risk and found incidences of 1.5%, 5% and 15% at 10, 20 and 30 years after treatment with radiotherapy, compared to 1.5%, 1.5% and 4% for those treated with chemotherapy alone. Furthermore, we found a SIR of 5.2 for BCC, resulting in 53 excess cases of BCC per 10.000 persons per year in our HL cohort, when compared to the general population in the Netherlands. As BCC are not registered in the Netherlands Cancer Registry we compared our data to population data from Cancer Registry of the Comprehensive Cancer Center South (CCCS), which is the only registry of BCC incidence in the Netherlands. The increased rates found in our study are comparable those found by Swerdlow *et al.*

(17). When assessing location-specific rates we found increased rates in the chest and trunk area. This observation can be explained by the fact that most patients received radiotherapy to that area either as part of a mantle field or involved field irradiation. The high rates of BCC found in the not otherwise specified (NOS) group are due to the fact that our cohort had more missing anatomic locations than the CCCS registry. With respect to the effect of treatment, data showed the highest rates of BCC in those treated with radiotherapy alone. The lower, but still significantly increased, rates found in the combined modality group, could be due to the fact that these patients were more often treated with smaller, radiotherapy fields.

Several mechanisms for development of radiation-induced malignant neoplasms have been postulated (23). Ionizing radiation can result in sublethal DNA damage which could cause genetic changes. These changes may contribute to malignant transformation in the irradiated tissues, even after low doses of irradiation. This might explain the increased incidence of skin cancers in patients who received RT as (part of) their treatment. The observed interval of 15 years and more for increased risks of developing skin cancers was also found in other studies reporting on secondary malignancies after cancer treatment. Since the majority of our HL cohort has not yet reached a follow-up duration over 15 years, and absolute risks of developing skin cancer increase with older age, the total number of skin cancers is expected to further increase in the upcoming years, implicating a substantial and clinically relevant problem.

Due to the retrospective nature of our study, certain potential confounding factors could not be evaluated. Smoking habits, (work-related) sun exposure, age, light skin type or family history are established risk factors for developing BCC (24-26), which were by far the most frequent skin cancers in our cohort. One patient in our cohort developed a total of 44 subsequent skin cancers in a time period of 20 years. An influence of genetic predisposition for developing skin cancer can therefore not be ruled out. Since medical records of patients in our cohort were often incomplete for skin cancer risk factors other than radiation, our data could not be analyzed with adjustment for these risk factors. It is unlikely, however, that these factors would differ considerably between patients receiving radiotherapy and those who were treated with chemotherapy alone. Given the median time interval of 18 years to development of the first skin cancer after primary treatment, a retrospective study is probably the only feasible type of research for this purpose.

To ensure an independent and complete report on the development of skin cancers in our cohort we used the PALGA database for histological confirmation. In principle it could be that some skin cancers, mainly BCC, were treated without histological confirmation. Therefore it is possible that the observed incidence rates in our cohort slightly underestimate the true occurrence of BCC.

Radiotherapy has played an important role in HL treatment since the 1960s. Extended field radiotherapy has long been (part of) standard treatment. Such extended fields exposed large parts of the patient's body to radiation. Current combined treatment approaches for early stage HL with 3-4 cycles of chemotherapy followed by lower doses of involved field radiotherapy, and more recently involved node radiotherapy, have resulted in significantly reduced irradiated volumes (27, 28). Complete omission of radiotherapy in early stage HL has been shown to lead to increased local relapse rates (29, 30). With radiotherapy as an important element in the treatment of HL, patients will continue to be at risk for late adverse events due to their treatment. Patient and doctor awareness of the increased risk of developing skin cancers in addition to the established risk of secondary solid tumors such as breast cancer, lung cancer or gastrointestinal cancers is therefore essential (31-33). Increased awareness will lead to reduced morbidity by means of preventive measures (such as reduction of sun exposure) and early detection (34-36). In this light, a nationwide network of specialized long-term HL follow-up clinics has been started in the Netherlands, to ensure optimal patient education, aimed at prevention and early detection of late treatment sequelae (37).

In conclusion, our cohort study shows a substantially increased risk of secondary skin cancers in HL survivors receiving radiotherapy as part of their treatment, both compared to the general Dutch population and to those treated with chemotherapy alone. This excess risk remains increased for at least 35 years after treatment. Patients and health care providers should be aware of this risk, in order to facilitate preventive measures and rapid access to early diagnosis and treatment.

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chapter 3

Screening for coronary artery disease after mediastinal irradiation in Hodgkin lymphoma survivors: phase II study of indication and acceptance

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Abstract

Background
Cardiovascular diseases are the most common nonmalignant cause of death in Hodgkin lymphoma (HL) survivors, especially after mediastinal irradiation. We investigated the role of computed tomographic coronary angiography (CTA) as a screening tool for coronary artery disease (CAD) in asymptomatic HL survivors, and related CTA findings to exercise testing and subsequent interventions.

Patients and methods
Patients were eligible for this phase II study if at least 10 years disease-free and treated with mediastinal radiotherapy. Screening consisted of electrocardiogram, exercise testing and CTA. Primary endpoint was significant CAD (stenosis >50%) on CTA. CTA screening was considered to be indicated for testing in a larger population if $\geq$ 6 out of 50 CTA scanned patients (12%) would need revascularization. Screening was evaluated with a questionnaire before and after screening.

Results
Fifty-two patients were included, and 48 patients underwent CTA. Median age was 47 years, time since HL diagnosis 21 years. There were 45 evaluable scans. Significant CAD on CTA was found in 20% (N=9), significantly increased compared with the 7% expected abnormalities (p=0.01, 95% CI 8.3-31.7%). In 11% (N=5) significant stenosis was confirmed at coronary angiography, and revascularization was carried out. Additionally, two patients were treated with optimal medical therapy. Ninety percent of patients were content with screening, regardless whether the CTA showed abnormalities.

Conclusions
Prevalence of significant CAD among HL survivors is high, while asymptomatic even in the presence of life-threatening CAD. This might justify screening by CTA in asymptomatic HL survivors who had mediastinal radiotherapy, but needs to be evaluated in a larger cohort.

Introduction

Over the past 30 years, disease-specific survival in Hodgkin lymphoma (HL) patients has increased dramatically due to improved treatment strategies. However, HL survivors remain at risk of developing late treatment sequelae resulting in increased morbidity and mortality. Cardiovascular diseases (CVD) are the most common non-malignant cause of death in these patients (1). A three- to fourfold increased risk of myocardial infarction due to coronary artery disease (CAD) has been observed, especially in HL survivors who had mediastinal irradiation as monotherapy or in combination with chemotherapy (2, 3). The course of CAD in HL survivors is often asymptomatic, even in the presence of severe stenosis (4). Traditional risk assessment therefore fails to identify HL survivors at high risk for myocardial infarction. More rigorous surveillance in this population seems warranted. The current gold standard for detecting CAD, invasive coronary angiography (CAG), is unsuitable for screening purposes due to risks of complications and mortality. A recent review of studies investigating noninvasive screening techniques for CAD in HL survivors reported disappointing test characteristics of exercise testing, with a reported sensitivity for significant CAD stenosis of only 59%. Moreover, 25% subsequently developed symptomatic CAD within a follow-up duration of 6.5 years (4). Recently, high diagnostic accuracy of screening with computed tomographic coronary angiography (CTA) has been shown in symptomatic patients at intermediate or high risk for CAD (5). A recent study using CTA as a screening tool for CAD among childhood survivors of HL showed a high prevalence of coronary abnormalities (6).

The purpose of this phase II study was to investigate the role of CTA as a screening tool for CAD in asymptomatic HL survivors who underwent mediastinal irradiation as part of their treatment, to relate CTA findings to electrocardiogram (ECG) exercise testing, and to determine the frequency and type of subsequent coronary interventions prompted by CTA. In addition, health-related quality of life (HRQL) and acceptance of screening among patients included in the study was evaluated, both before and after cardiac screening.

Methods

Patients

Long-term HL survivors treated at the departments of Radiation Oncology and Hematology at Leiden University Medical Center (LUMC) were invited to partici-

pate. Patients with all stages of HL who were at least 10 years disease-free and had received mediastinal radiotherapy as part of their treatment were eligible. Exclusion criteria were age >60 years; current treatment of CVD other than hypertension, dyslipidemia or minor valve defects; previous CTA in the past 2 years; renal function impairment; known contrast allergy and/or presence of a life-threatening disorder.

Study protocol

This was a single-institution phase II study. The trial protocol was approved by the LUMC Ethics Committee and registered with ClinicalTrials.gov, NCT01271127. After obtaining written informed consent, information on patient and treatment characteristics including radiation treatment fields and dose, and type and dose of (anthracycline-containing) chemotherapy were collected from patient files. Patients were referred to the Cardiology Outpatient Clinic for extensive cardiovascular screening. This included a detailed patient history focusing on specific symptoms and risk factors for CVD, physical examination, fractionated serum cholesterol and glucose testing, resting ECG, echocardiography and symptom-limited exercise ECG testing (7). At a separate visit, cardiac CTA imaging was carried out using a 320-detector row volumetric scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) according to standard clinical practice (8). Patients with a heart rate above 65 beats/min received 50 or 100 mg metoprolol orally 1 h before imaging, unless contraindicated. In addition, sublingual nitroglycerin (0.4 or 0.8 mg sublingual) was administered 5 min before the start of the scan (9). Noncontrast-enhanced and contrast-enhanced scans were carried out. The nonenhanced scans were used to assess the total amount of coronary artery calcium score according to Agatston (10). CTA datasets were evaluated for plaque constitution in a consensus reading by two experienced observers, who were aware of the patients history regarding radiation treatment, but not of any possible current symptoms. Results of CTA were classified as normal (<30% luminal narrowing), nonsignificant CAD (30-50% luminal narrowing) or significant CAD (>50% luminal narrowing).

Results of all examinations and potential indications for further analysis or treatment were discussed during a subsequent visit. If a significant coronary stenosis was observed on CTA, diagnostic coronary angiography was carried out, according to standard LUMC Cardiology protocols.

Assessment of HRQL

Patients were asked to complete three validated HRQL questionnaires at baseline and at completion of the study. The EORTC QLQ C-30 questionnaire measures health-related quality of life (11). The EORTC INFO-25 measures patient satisfaction with regard to received information on treatment (12); and the FAS (fatigue assessment scale) is a rating scale for fatigue and loss of energy (13). An additional short questionnaire of nine items, designed specifically to evaluate acceptance of screening, was added (see appendix Chapter 4).

Study design

Primary endpoint was the presence of significant CAD ($>$ 50% stenosis) on CTA. With an estimated rate of 7% significant coronary disease in asymptomatic healthy individuals (14), and increased relative risk of three in HL survivors (2), we expected to identify significant coronary stenoses in 20-25% of our HL population. A sample size of 50 patients would achieve $\geq$80% power to detect a threefold relative increase of 7% to 20%, and thus an absolute increased risk of 13%, using a two-sided binominal test with $\alpha \leq 0.05$. With an expected prevalence of significant coronary stenoses of 20%, it is assumed that 10 out of 50 scans will demonstrate significant CAD. Allowing for false-positive scans, we considered CTA screening to be indicated for testing in a larger population if in $\geq$ 6 patients out of 50 CTA scanned patients (12%) revascularization would be indicated.

Secondary objectives were to determine the frequency and type of subsequent interventions, to compare CTA findings to exercise ECG testing results, to evaluate HRQL and acceptance of screening, and to compare prevalence and location of coronary artery stenoses to CTA findings from an age, sex and risk factor matched control population.

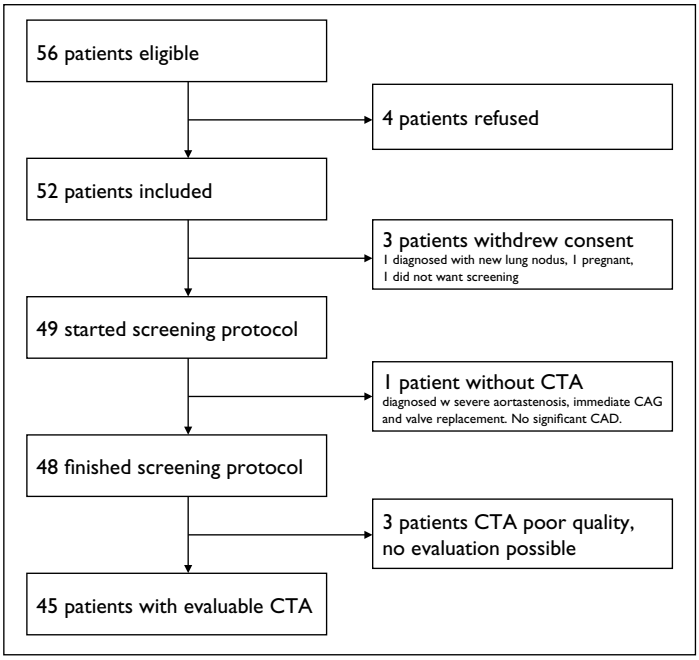

Figure 3.1: CONSORT diagram for CTA analysis

Statistical analysis

All statistical analyses were performed using SPSS statistical software for windows version 20. For the analysis of the primary endpoint all patients with evaluable CTAs were included. Analyses of secondary objectives were done in a descriptive manner. Evaluation of HRQL was done by using EORTC guidelines (15). Prevalence, location and aspect of CAD in our study population were compared to sex, cardiac risk factor and age-matched cases from an ongoing CTA registry at the LUMC Cardiology Department containing CTA results from >1000 patients presenting with chest pain who underwent cardiac evaluation.

Results

Patients were included between January 2011 and March 2012 (Figure 3.1).

Among the 52 included patients, 3 withdrew after signing informed consent. One patient did not undergo CTA due to immediate intervention for severe aortic valve stenosis. The remaining 48 patients completed the screening protocol. Characteristics of the 48 patients finishing the CTA screening protocol are summarized in Table 3.1. Median age was 47 years (range 29-60 years), 60% was female. Thirteen patients (27%) had been treated with radiotherapy as monotherapy, 35 with combined modality treatment. Median dose of mediastinal radiotherapy was 36 Gy (range 24-40 Gy). Radiotherapy volumes most frequently used were involved field in 25 patients, mantle fields (mediastinal and axillary fields) in 11 and subtotal nodal fields (mediastinal, axillary, para-aortic and splenic fields) in 9.

Nine patients received a cumulative anthracycline dose of $\geq$300 mg/m2 (median dose 360 mg/m2). Most patients had no risk factors for developing CAD; the risk factor most frequently reported was Body Mass Index (BMI) >25, which was present in 19 patients (median BMI 27 kg/m2). Detailed treatment characteristics of patients with abnormal CTA results are described Table 3.2.

CTA results

In total, 48 patients underwent CTA. Due to increased heart rates resistant to β-blocking agents and resulting in motion artefacts on CTA, three scans were not evaluable. Another 12 scans were of suboptimal quality, due to the same problem, but were of sufficient quality for evaluation. In the 45 scans available for assessment, the prevalence rate of significant CAD on CTA was 20% (N=9, p=0.01, 95% CI 8.3 - 31.7%) and thus significantly increased compared with the expected population prevalence rate of 7%. Eight of nine patients with significant CAD on CTA were classified as having a low risk for developing CAD, according to the Framingham Risk Score (16). Eight patients with significant CAD on CTA underwent CAG. In five of these patients significant proximal CAD was confirmed and revascularization procedures carried out, among which two coronary artery bypass grafts for severe left main artery stenosis. The remaining three patients did not need revascularization, but two were started on drug therapy with statins and platelet inhibition (Table 3.3). Accuracy of CTA, defined as the confirmation of abnormalities on CAG resulting in a subsequent intervention was 88% (seven out eight patients who underwent CAG). One patient with possibly significant CAD on CTA refused subsequent CAG, since she had been

Table 3.1: Patient and treatment characteristics

	Number of patients	%
Total	48	
Sex	Number of patients	%
Male	19	40
Female	29	60
Age and time interval	Years	Range
Median age at diagnosis HL	26	(15-37)
Median age at time of study	47	29-60
Median time since diagnosis	21	11-29
Stage (Ann-Arbor)	Number of patients	%
I	8	17
II	34	71
III	4	8
IV	2	4
Treatment	Number of patients	%
Median dose mediastinal radiotherapy (range)	36 (24-40)	
Number of patients receiving combined modality treatment	35	73
Number of patients >300 mg/mm2 anthracycline	9	19
Chemotherapy regimes	Number of patients	%
MOPP	5	14
MOPP-ABV	12	34
ABVD	10	29
EBVP	5	14
BEACOPP	3	9
Cardiovascular risk factors	Number of patients	%
Cigarette smoking	4	8
Hypertension	4	8
Diabetes mellitus	0	0
Dyslipidaemia	6	13
Family history positive for myocardial infarction	8	16
Body mass index >25	19	40

MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MOPP-ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; EBVP = epirubicin, bleomycin, vinblastine and prednisone; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

Table 3.2: Characteristics of patients with abnormal CTA results

Sex	Current age (yrs)	Time since diagnosis (yrs)	Stage	Chemotherapy	RT fields	Dose mediastinum (Gy)	Risk factors	CAG	Findings CAG	Intervention
F	46	18	2	No	STNI	36	HT, Family	yes	30% stenosis proximal LM	Platelet inhibition Statins
M	55	25	2	3.5 x ABVD	Mantle	36	Smoking, HC, Family	yes	80% stenosis mid RCx total occlusion proximal RCA	Revascularization PCI
F	51	26	2	No	STNI	36	-	no	-	-
M	51	25	2	6 x ABVD	Mantle	40	BMI 28	yes	40% stenosis proximal RCx, RCA	-
F	56	29	3	6 x MOPP	Mantle	35	-	yes	70% stenosis ostium RCA	Revascularization PCI
M	49	21	2	6 x MOPP/ABV	IF	40	-	yes	90% stenosis LM 40-50% stenosis proximal RCA	Revascularization CABG
M	49	29	1	No	Mantle	40	BMI 27	yes	>90% stenosis ostium RCA	Revascularization PCI
M	55	24	1	No	Mantle+PaO	36	-	yes	diffuse arthrosclerosis, no significant stenosis	Platelet inhibition Statins
F	52	18	2	3 x MOPP/ABV	IF	36	-	yes	70-80% stenosis LM	Revascularization CABG

RT = radiotherapy; CAG = coronary angiography; F = female; M = male; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MOPP/ABV = mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine; STNI = subtotal nodal irradiation; Mantle = mantle field; IF = involved field; Mantle + PaO = mantle field + para-aortic nodes; HT = hypertension; HC = hypercholesterolemia; Family = family history positive for ischemic heart disease; BMI = body mass index; LM = left main artery; RCx = ramus circumflexis; RCA = right coronary artery; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

diagnosed with breast cancer at the time of CTA. Patients with significant CAD on CTA more often had high calcium scores (75^{th}–100^{th} percentile) than patients who had no severe abnormalities on the CTA scan (55% compared to 17%, Table 3.3).

Matched case-controls

For the nine patients in our study with significant CAD on CTA, the LUMC Cardiology database was searched for matched cases. Due to young age and absence of risk factors in the HL survivors, only a single matching case could be found.

Among the HL patients with CAD on CTA 78% (seven of nine) were treated, either with optimal medical treatment or intervention, while in the matched cases eventually only 22% (two of nine) had significant CAD on CTA necessitating treatment. These small numbers impaired comparison of location or aspect of coronary stenosis.

Exercise ECG testing versus CTA

Results from ECG exercise testing were related to findings on CTA (Figure 3.2). Of the 48 patients that started the screening protocol, 3 were not able to perform an exercise test due to physical impairments. These three patients had no signs of significant CAD on CTA. The remaining 45 patients underwent both ECG exercise testing and CTA. None of the patients had complaints of angina pectoris during the test. Three patients had signs of ischemia on ECG during exercise testing. Presence of significant CAD was found in only one of them. Of the 42 patients with a normal exercise test, 8 had significant CAD on CTA and CAG was carried out in 7. Revascularization was needed in four, and two were started on drug therapy. The two patients with severe left main artery stenosis on CTA and CAG showed no signs of ischemia during the ECG exercise test.

HRQL and acceptance of screening

Forty-seven patients (98%) participated in the HRQL part of this study and completed the first set of questionnaires; 40 completed the second questionnaires, resulting in a response rate of 85%. All patients who underwent CAG returned both questionnaires. Of all patients 90% responded with 'quite a bit' or 'very much' to the question whether

Table 3.3: Patients with coronary artery disease detected at CT Coronary Angiography: calcium scores and subsequent interventions

Patient	FRS	Risk Profile	Exercise testing	Ca score	Percentile	CTA	CAG	Findings CAG	Intervention
F, 46 yr	2%	low	no ischemia	1	50-75	Possible stenosis LM	yes	30% stenosis proximal LM	Platelet inhibition Statins
M, 55 yr	20%	IM	abnormal	438	90-100	Significant stenosis proximal RCx, Total occlusion proximal RCA	yes	80% stenosis mid RCx total occlusion proximal RCA	Revascularization PCI
F, 51 yr	4%	low	no ischemia	69	75-90	Possible stenosis mid RCx	no	-	-
M, 51 yr	7%	low	no ischemia	512	90-100	3-vessel disease	yes	40% stenosis proximal RCx, RCA	-
F, 56 yr	4%	low	no ischemia	466	90-100	50% plaque proximal LAD	yes	70% stenosis ostium RCA	Revascularization PCI
M, 49 yr	7%	low	no ischemia	0	-	60% stenosis ostium LM	yes	90% stenosis LM 40-50% stenosis proximal RCA	Revascularization CABG
M, 49 yr	7%	low	no ischemia	12	50-75	Possible stenosis ostium RCA	yes	>90% stenosis ostium RCA	Revascularization PCI
M, 55 yr	7%	low	no ischemia	1112	90-100	Diffuse extensive arthrosclerosis	yes	diffuse arthrosclerosis, no significant stenoses	Platelet inhibition Statins
F, 52 yr	5%	low	no ischemia	14	50-75	70% stenosis proximal LM	yes	70-80% stenosis LM	Revascularization CABG

F = female; M = male FRS = 10 yr risk of Coronary Heart Disease according to Framingham Risk Score (16); Risk Profile = classification of FRS into low (<10%), intermediate (IM) (10-20%) and high (>20%) categories for 10-year risk of developing CAD (16); Ca score = total score of calcifications in coronary arteries according to the Agatston approach (10); Percentile = reference of calcium score to individuals of the same age and gender; CTA = Computed Tomography Coronary Angiography; CAG = coronary angiography; LM = left main artery; RCx = ramus circumflexus; LAD = left anterior descending; RCA = right coronary artery; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

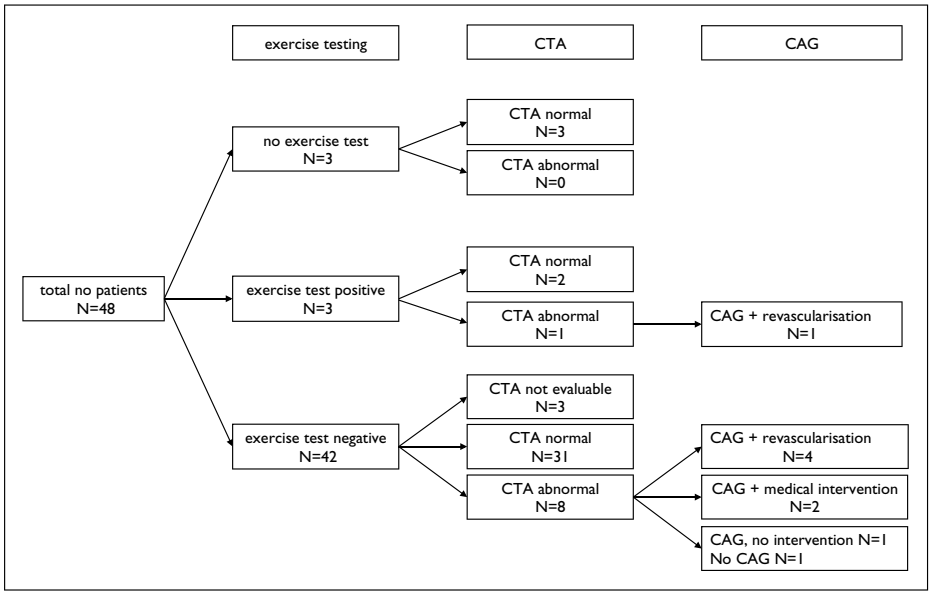

Figure 3.2: Results of exercise ECG testing versus CTA

they were content with participating in the screening study. Visiting the cardiac outpatient clinic and undergoing the CTA was perceived cumbersome by 10% and 20% respectively.

The emphasis that was placed on the possible cardiac effects of treatment of HL was perceived as bothersome by 25%. Full analysis of HRQL will be described in a separate publication.

Discussion

This phase II study investigated the role of CTA as a screening modality for CAD in asymptomatic HL survivors. We detected a 20% prevalence rate of significant ostial or proximal coronary artery stenosis on CTA, the majority of which was confirmed with CAG. Another 22% (N=10) of the study population had an abnormal CTA, with nonsignificant stenosis (30-50%) in the proximal coronary arteries.

Prevalence of CAD on CTA was high, especially considering the fact that almost all patients were categorized as having a low risk for developing CAD, based on young age and absence of risk factors such as smoking or dyslipidemia. Comparing the HL patients to matched cases proved to be difficult, which underlines the fact that HL survivors do not fit the usual high-risk cardiac profile. Only a small proportion of the HL survivors had received a cardiotoxic cumulative dose of chemotherapy, suggesting that previous radiation treatment may be the most probable cause of CAD. The prevalence of coronary stenosis found in this study is likely to be an underestimation of the true occurrence of CVD, since patients with already apparent CAD were ineligible.

In our study, 5 of the 45 evaluable patients (11%), close to the predefined 12%, underwent revascularization procedures. Another two were treated with optimal medical therapy, resulting in a prevalence rate of patients with severe abnormalities needing interventions of 16% (7 of 45). One patient did not complete screening due to immediate treatment of severe aortic valve stenosis.

The potential role of CTA as a screening tool for CAD in asymptomatic HL survivors was tested in two other studies. In a small pilot study including nine patients with a treatment history of mediastinal radiotherapy and a median follow-up duration of 26 years, Rademaker *et al.* found five patients with stenoses >50%, of whom 2 were subjected to CAG and required revascularization. However, in this study most patients had additional risk factors for developing CAD (17). Kupeli screened 119 childhood HL survivors of whom 50% had received mediastinal radiotherapy (median dose 27.5 Gy) after a relatively short median follow-up period of 10 years. Abnormalities on CTA were found in 16%, but only one patient underwent subsequent CAG (6). Although the number of patients in our pilot study is limited, one of the strengths is that in almost all patients with significant stenosis on CTA CAG was carried out to confirm CTA results.

Our study compared different types of noninvasive screening. Only one patient with significant CAD was accurately identified by ECG exercise testing, and none of the participating patients reported symptoms, not even in the presence of severe CAD. These observations confirm the limited value of screening by means of ECG exercise testing in this setting as reported in the literature (2).

Considering these results, and with the knowledge that it has been demonstrated that the predictive value of a negative CTA is high for excluding CAD and correlates with a low risk of cardiac death in the near future (18), it seems justified to conclude that CTA is an effective, and possibly the most suitable noninvasive screening modality for CAD in asymptomatic HL survivors.

CTA screening and cardiac intervention in this population might be advisable, provided that treatment that improves outcome for those with screen-detected ab-

normalities is available. Survival benefit of cardiac interventions has been demonstrated in high risk symptomatic cardiac patients (19). The CASS study also showed a 30% increase in overall survival in asymptomatic patients treated for proximal left CAD (20). In our patients, all significant stenosis were located in the ostium or proximal in the coronary arteries, resulting in a large cardiac area at risk at the event of occlusion.

Screening and cardiac intervention in asymptomatic HL survivors might therefore also be indicated, but this should be evaluated in larger cohort studies, as it is unlikely that randomized trials will be feasible in this setting. Our study showed that acceptance of screening was high. Regardless whether CTA showed abnormalities or not, 90% was content with the screening study and with being informed on the risk of late cardiac events. In view of the broad acceptance of screening and the high rate of CAD stenoses found in this phase II study, a nationwide study to establish the role of CTA-based cardiac screening in a large population of asymptomatic HL survivors treated with mediastinal radiotherapy should be considered. This could also provide more clarity on timing and frequency of screening, costs of screening and possible effects of screening on HRQL. Positive findings of screening should also be balanced against possible disadvantages such as additional radiation exposure and the risk of complications due to invasive diagnostic procedures.

At LUMC β-blockers are given prior to CTA imaging to optimize image quality. However, a remarkably large proportion of the participants (31%) had elevated heart rates unresponsive to β-blocking agents. This led to non-evaluable CTA scans in three patients, and suboptimal quality images in another 12 patients. Further research on the pathophysiology of this tachycardia will be conducted.

In conclusion, prevalence of severe CAD in asymptomatic long-term HL survivors treated with mediastinal irradiation is significantly increased, and very often asymptomatic, even in the presence of a severe proximal stenosis. This might justify screening by CTA to reduce the risk of life-threatening cardiac events in this population, but the role of CTA-based cardiac screening needs to be evaluated in larger cohort studies.

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chapter 4

Impact of cardiovascular counseling and screening in Hodgkin lymphoma survivors

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Abstract

Purpose
Cardiovascular disease (CVD) is the most common nonmalignant cause of death in Hodgkin lymphoma (HL) survivors, especially after mediastinal irradiation. The role of screening for CVD in HL survivors is unclear, but confrontation with risks of CVD may have a negative influence on health-related quality of life (HRQL). As part of a phase II screening study using computed tomography angiography (CTA) among HL survivors, a HRQL analysis was done to evaluate the emotional and practical burden and perceived benefits of screening and the effect of CVD-specific counseling on patient satisfaction.

Methods
Patients who participated in the screening study took also part in the HRQL study. The impact of undergoing screening was evaluated with a 9-item questionnaire, and impact on HRQL with the EORTC QLQ-C30. The effect of counseling on CVD on perceived information provision was evaluated with the EORTC INFO-25.All questionnaires were completed at baseline and after screening.

Results
Baseline questionnaires were received from 48 participants, and 43 completed questionnaires after screening. Mean age was 47 years, mean time since diagnosis 21 years. 93% were content with participating, and 80% did not find the emphasis placed on late effects burdensome, although screening did have a small impact on social functioning and global quality of life.

Perceived information on disease, medical tests and treatment increased significantly after screening ($p<0.01$). Differences were clinically relevant. There were no differences in perceived information between patients with and without screen-detected CVD.

Conclusions
Screening was evaluated favorably, whether CTA showed abnormalities or not. Extensive counseling resulted in substantially increased information provision, resulting in improved information satisfaction. Screening by means of CTA and subsequent cardiac intervention was highly valued and the benefits were felt to outweigh the emotional and practical burden.

Introduction

The outlook for cure of Hodgkin lymphoma (HL) patients has improved dramatically due to modern chemotherapy and improved radiotherapy techniques (1-3). However, over the past decade it has become evident that cure may come at a price. Epidemiological studies have shown that survivors of HL are at serious risk for late treatment effects, such as an increased risk of long-term risk of secondary cancers (4, 5). The most common nonmalignant long-term complication of treatment in HL survivors is cardiovascular disease (CVD). HL survivors who had mediastinal radiotherapy have a 3-4 fold increased risk of myocardial infarction due to coronary artery disease (CAD) (6-9). Even severe CAD is often not accompanied by symptoms, and can occur in absence of traditional risk factors (10).

The role of screening for radiation-induced CAD in HL survivors is unclear. Several prospective studies have shown that screening asymptomatic HL survivors by means of computed tomographic coronary angiography (CTA) yields high prevalence rates of CAD (11-13).

However, the benefit of screening on survival is unknown. Also, the perceived burden and distress of undergoing screening, and the effect of cardiovascular counseling on health-related quality of life (HRQL) have not been studied in HL survivors. Confrontation with possible risks of disease may have a negative effect on psychosocial well-being. This effect has been shown in screening programs for breast cancer (14). However, other studies have shown that empowering patients by improving information provision and thus disease understanding might actually improve HRQL (15).

To investigate the role of CTA as a screening tool, we have conducted a phase II screening study in asymptomatic HL survivors at risk for developing radiation-induced CAD (16). We included a HRQL analysis to determine the perceived burden of screening, and evaluate whether extensive counseling on risks of CVD improved perceived information provision and patient satisfaction.

Methods

Patients

The study protocol for this phase II screening protocol was approved by the Leiden University Medical Center (LUMC) Ethics Committee and registered with Clinical-

Trials.gov, NCT01271127. Since 2010 long-term HL survivors from regular follow-up outpatient clinics at the Department of Radiation Oncology at LUMC are referred to an outpatient clinic specifically designed for monitoring late effects of treatment of HL. At this outpatient clinic two dedicated radiation oncologists and one hematologist counsel HL survivors who are at least 5 years disease-free after treatment with respect to individual risks of late treatment effects, and provide standardized follow-up care, including screening for breast cancer in female HL survivors.

To address the feasibility of cardiac screening by means of CTA and evaluate the perceived burden and benefits of screening a phase II study was designed. Patients attending the late effects outpatient clinic who were at least 10 years disease free and had received mediastinal radiotherapy as part of their treatment, who were $<$ 60 years, and without current serious cardiac disease were eligible, and invited to participate in the study.

Primary endpoint of the phase II study was the presence of significant CAD ($>$ 50% stenosis) on CTA. Patients with abnormal CTA scans subsequently underwent diagnostic coronary angiography (CAG). CTA screening was considered to be indicated for testing in a larger population if revascularization would be indicated in $\geq$ 12% of the patients undergoing CTA. Secondary objectives were to determine the frequency and type of subsequent interventions, to evaluate satisfaction with information provision and to determine the burden of the various aspects of screening and the impact of specific counseling on CVD on HRQL.

Counseling, screening and assessment of HRQL

Participants in the screening study received specific, in-depth counseling on the risk of developing radiation-induced CVD by a dedicated radiation oncologist. After written informed consent, patients were referred to the cardiology outpatient clinic where they received additional counseling and lifestyle advice to reduce the risk of future cardiac disorders by a cardiologist. Subsequently an extensive cardiovascular screening program was performed. This included a resting electrocardiogram (ECG), echocardiography and symptom-limited exercise ECG testing. CTA was performed in a separate visit. After completing all tests, results and potential indications for future analysis or treatment were discussed. Participation in the HRQL part of the screening study was not mandatory for inclusion in the cardiac screening program.

For the HRQL part, patients were asked to complete three validated questionnaires at baseline and after discussing test results or subsequent interventions; a 9-item screening-specific questionnaire was added to the end-of-screening questionnaire. Baseline questionnaires were handed out at the time patients were asked to

participate in the screening study and were returned prior to referral to the Cardiology Department. End of study questionnaires were sent out 1-2 months after the final visit to the Cardiology department.

Questionnaires

To evaluate the effect of cardiovascular counseling and screening on information provision the EORTC INFO-25 questionnaire was used. This module evaluates cancer patient satisfaction with regard to information received in different areas of their disease and treatment, and evaluates qualitative aspects (17, 18). The 25 items are organized in four multi-item scales and single items. After linear transformation, all scores range from 0-100 (19). High scores mean a high level of information received (17).

Global quality of life was assessed with the EORTC quality of life core questionnaire (QLQ C-30 v3.0). All subscales and symptom responses from this questionnaire are linearly converted to 0 to 100 scales (19). A higher score for a functional or global quality of life scale represents a better level of functioning.

Fatigue was measured with the fatigue assessment scale (FAS); a validated 10 item questionnaire reflecting mental and physical fatigue (20, 21).Total scores ranged from 10 to 50. A higher score reflects a higher level of fatigue. A score over 21 points indicates a substantial level of fatigue (20).

Evaluation of screening

To evaluate the burden of the various aspects of screening, and determine satisfaction with the screening procedures an additional short questionnaire containing 9 items was designed (appendix). The first three questions evaluated the burden of the two separate visits that were made as part of the screening protocol, and the psychological impact of waiting for test results. The emphasis placed on late treatment effects due to screening might be perceived as distressing, which was evaluated in question 4. The fifth question evaluated whether participants felt well informed with regard to the purpose of the screening program. The last part of the questionnaire evaluated patient satisfaction with several aspects of the screening study to assess whether participants were sufficiently prepared for the procedures of the screening tests, and were content with the aftercare. The final question evaluated satisfaction with participating in the study in general.

Statistical analysis

All statistical analysis were performed using SPSS statistical software for windows version 20 (SPSS inc., Chicago, IL). Results of the evaluation of screening questionnaire and differences between participants with and without significant CAD on CTA were analysed using the χ^2 test for trend.

The EORTC INFO-25 and QLQ-C30 questionnaires were analysed according to EORTC guidelines (22). For partially incomplete questionnaires imputation of the mean was used for scales containing at least 50% of the scores (22).

To test for significant changes in perceived information provision, fatigue or global quality of life between start and end of the screening study, results were compared using a paired t test. Clinical relevance of changes was defined according to published guidelines. For the EORTC INFO-25 a difference in score $\geq$ 10 points indicates a clinically relevant difference (23). Multivariate linear regression analysis was performed to investigate independent associations between socio-demographic, clinical characteristics and abnormalities on CTA with differences in perceived information provision, fatigue and general QoL over time. P-values of <0.05 were considered statistically significant.

Results

Patients and compliance

In the screening study, 49 patients started the screening protocol between January 2011 and March 2012. In total, 48 patients finished the screening protocol, all of whom underwent CTA. One patient did not complete the screening protocol, due to immediate intervention for severe aortic valve stenosis. Due to increased heart rates resistant to beta blocking agents and resulting in motion artefacts on CTA, 3 scans were not evaluable. In the 45 patients with evaluable CTA scans abnormalities were found in 9 patients (20%), of whom 7 needed intervention (16).

Baseline HRQL questionnaires were received from 48 patients starting the screening protocol (98%). End of study questionnaires were filled out by 43 patients (91%) finishing the study protocol (Figure 4.1). Because the 3 patients with non-evaluable

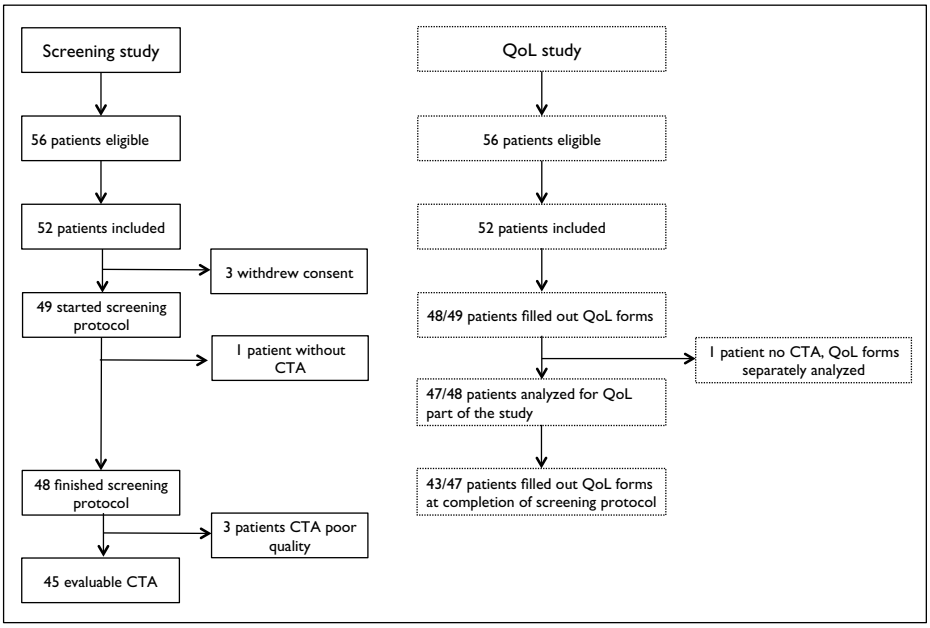

Figure 4.1: Consort diagram of screening study and quality of life study.

CTA scans did complete the entire screening protocol, they were included in the HRQL analysis. The four patients who did not return end of study questionnaires were two males and two females, all of whom had no abnormalities on CTA.

Returned questionnaires were complete for all items in 84% of the EORTC INFO-25, 99% of the EORTC QLQ-C30, 97% of the FAS and 94% of the evaluation of screening questionnaire.

Mean age of participants of the HRQL study was 47 years, mean time since diagnosis was 21 years. Most patients (70%) had been treated with combined modality treatment, and 16% had received >300 mg/m^2 anthracycline in their chemotherapy. Most patients (51%) had a high level of education, and 77% were currently employed (Table 4.1).

Table 4.1: Characteristics of health-related quality of life study participants

	Number of patients	%
Total	43	
Sex	Number of patients	%
Male	16	37
Female	27	63
Age and time interval	Years	Range
Median age at diagnosis HL	26	15-37
Median age at time of study	47	29-60
Median time since diagnosis	21	11-29
Stage (Ann-Arbor)	Number of patients	%
I	7	16
II	30	70
III	4	9
IV	2	5
Treatment	Number of patients	%
Median dose mediastinal radiotherapy (range)	36 (24-40)	
Number of patients receiving combined modality treatment	30	70
Number of patients receiving >300 mg/mm^2 anthracycline	7	16
Marriage status	Number of patients	%
Single	3	7
Living with partner or married	36	84
Living with other family/children	4	9
Level of education	Number of patients*	%
Low	5	12
Intermediate	16	37
High	22	51
Employment status	Number of patients	%
Employed	33	77
Unemployed	6	14
Incapacitated	4	9
Cardiovascular risk factors	Number of patients	%
Current cigarette smoking	3	7
Hypertension	4	9
Diabetes mellitus	0	0
Dyslipidaemia	3	7
Family history positive for myocardial infarction	7	16
Body mass index >25	16	37

* Education levels: low = none/primary school, intermediate = lower general secondary education / vocational training, high = pre-university training / high level vocational training or university.

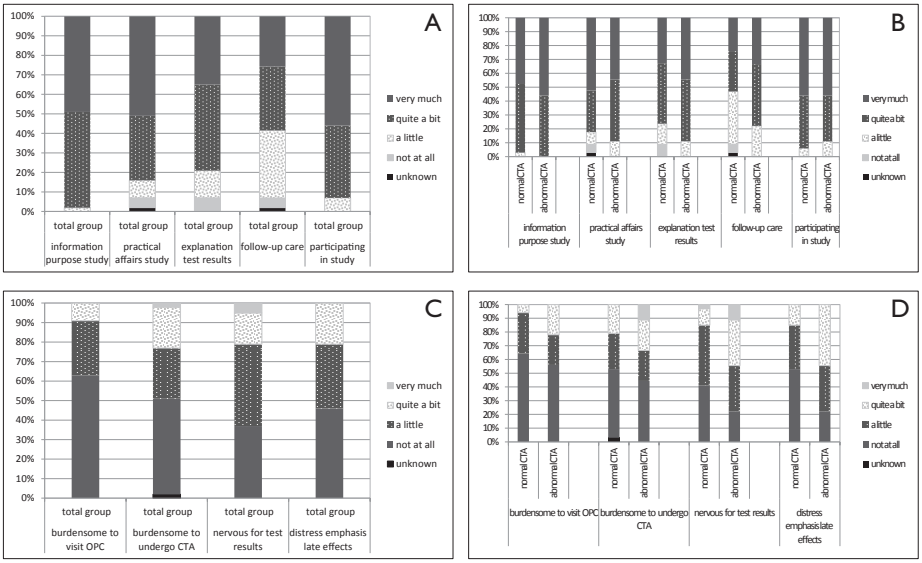

Figure 4.2: Patient responses to evaluation of screening questionnaire regarding practical aspects and perceived burden. A/B represent the results of the first five questions evaluating satisfaction with several aspects of the screening protocol, both fot the total group (A) and split by group of patients with and without abnormalities on CTA (B). C/D represents the perceived burden of various aspects of the screening program, both for the total group (C) and seperately for patients with and without abnormalities on CTA (D).

Evaluation of screening

Visiting the outpatient Cardiology clinic was perceived as not or a little bothersome by 91% of the participants. Undergoing CTA was perceived as bothersome by 24%, and 20% felt nervous before receiving the test results. Overall, 80% did not perceive the emphasis that was placed on possible late cardiac effects of treatment for HL by this screening study as bothersome (Figure 4.2A+C).

Patient satisfaction with participating in the screening study was high; 98% felt they were well informed about the purpose of the study, and 86% were content with the practical affairs concerning the study. Although 80% were satisfied with information and explanation of test results, 40% felt follow-up care should be improved. Overall, 93% were highly satisfied with participating in the study (Figure 4.2A+C).

Differences in the evaluation of screening questionnaire between participants with and without abnormalities on CTA were small and not statistically significant.

However, patients with abnormal CTA scans more often answered the question "how distressing is the emphasis placed on late effects" with "quite a bit" than participants with no abnormalities (44% vs 15%, p=0.70, Figure 4.2D).

Information provision and satisfaction, fatigue and global QoL

Results of the EORTC INFO-25 questionnaire showed that levels of information provision increased over time. Perceived levels of information concerning disease, medical tests, information on treatment and on other services such as possibilities for professional support were all significantly increased after completing the screening protocol, as compared to baseline (Figures 4.3A-D). Mean differences in scores between baseline and after screening were 19 (SD 17) points for information on disease, 40 (SD 21) points for information on medical tests and 26 (SD 15) points for information on treatment, indicating a substantial clinical relevance. Although the increase in perceived information on other services was less pronounced (from 2 to 12 points, Figure 4.3D), the difference was also clinically relevant.

Satisfaction with received information increased significantly from 20 to 48 points ($p<0.01$), a clinically relevant difference. Usefulness of given information also increased significantly, from 30 to 60 points ($p<0.01$).

There were no differences in levels of fatigue before or after the screening protocol (mean levels 21 points vs. 21 points, respectively). The number of patients indicating a substantial level of fatigue slightly increased from 13 (30%) to 15 (35%). The two new fatigue cases both had screening tests without abnormalities.

Results from the EORTC QLQ-C30 questionnaires are presented in Table 4.2. Role, physical, cognitive and emotional functioning did not change significantly over time. A small decrease in global health, from 75 points to 73 points, was found. The largest decrease was found in social functioning, from 88 points before screening to 82 points after completion, which reflects a small, clinically relevant difference.

Multivariate regression analysis did not show any significant associations between age, gender, level of education or abnormalities on CTA and perceived level of information, information satisfaction, fatigue or global health.

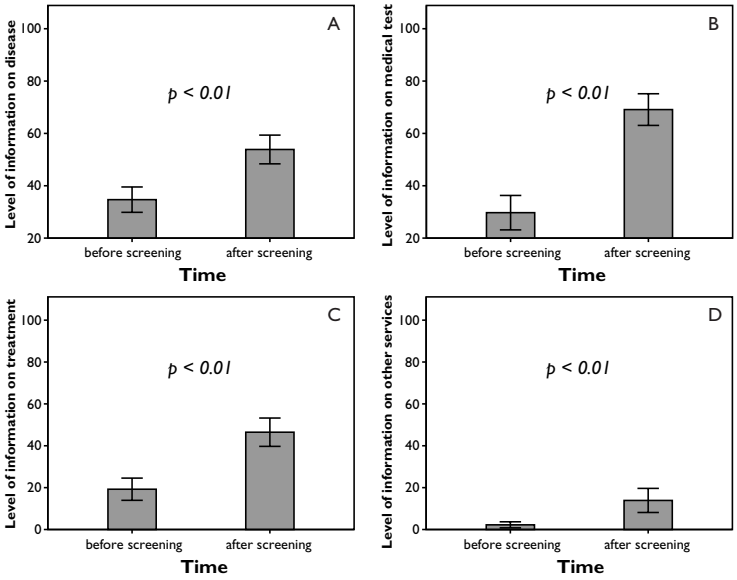

Figure 4.3: Patient responses to EORTC INFO-25 questionnaire. Mean levels of perceived information on disease (A), medical tests (B), treatment (C) and on other services (D) before start and after completing the screening program. A higher score indicates a higher level of perceived information. Error bars represent the 95% confidence intervals.

Table 4.2: Health-related quality of life and fatigue scores

	Before screening		After screening		P-value	Clinical relevance
	Mean	SD	Mean	SD		(23, 25)
QLQ C30						
Functional scales						
Role functioning	82	25	82	25	0.76	n.a.
Physical functioning	89	16	87	20	0.21	trivial
Cognitive functioning	84	21	82	21	0.43	trivial
Emotional functioning	81	18	82	21	0.73	trivial
Social functioning	88	20	82	27	0.03	small
Global health	76	20	72	20	0.04	small
FAS						
Total fatigue score	21.0	7.6	21.3	7.7	0.60	no

Results of the functional scale and global quality of life scores from the EORTC quality of life core questionnaire (EORTC QLQ-C30) and scores from the Fatigue Assessment Scale (FAS) both before and after screening.

Discussion

This analysis evaluated an extensive counseling and screening programme among HL survivors at risk for long-term cardiac sequelae of mediastinal radiotherapy, and assessed the effect on perceived information provision and satisfaction. Key findings of this study were that evaluation of screening was favorable, and did not differ between patients with and patients without abnormalities on the screening tests. Furthermore, perceived levels of information on disease, medical tests and treatment increased after counseling and completing the screening program, resulting in significantly improved satisfaction with information provision. Benefits of screening were felt to outweigh the burden.

Although several screening studies for radiation-induced cardiac disease have been performed, our study is the first to evaluate the psychological impact of cardiac screening on HL survivors, to assess the effect of counseling and screening on perceived information provision, and the first to evaluate HRQL both before and after screening (11-13). We showed the emphasis placed on possible late cardiac disorders due to treatment was not perceived as burdening. In fact, screening was highly valued by almost all participants in our 9-item specific questionnaire, thus indicating that perceived benefits outweigh the burden of screening, both in practical and emotional sense. Results from the validated QLQ-C30 questionnaire confirmed these results, showing no decrease in the emotional, cognitive or role functioning scales. However, counseling and screening did have a small impact on social functioning and perceived global health. We also showed that the combination of extensive information provision and screening translates into a clinically relevant improvement in perceived information and increased satisfaction with information provision. The difference found in the subscale 'information on other services' increased significantly after screening, but mean scores were still low. This could be explained by the fact that this aspect of information contains services such as information distributed on video or professional psychological support, which was not the main focus of the current study. Concerning fatigue and global quality of life, we found no significant differences between start and end of the study. This is not unexpected, considering the relatively short time interval in which the screening took place.

Eligible patients for this study were selected from the current follow-up population of HL survivors. Due to the increased risk of breast cancer prompting active screening, a large part of this population consists of females. This could explain the high percentage of female participants. Initially, almost all patients who participated in the screening protocol filled out baseline questionnaires. Compliance was high, as 91% also completed the set of questionnaires at the end of screening. The number of

missing items was limited. Therefore, the chances that the results were influenced by drop-out bias are small.

To evaluate whether the results of the cardiac tests influenced perceived information provision, fatigue or quality of life, multivariate regression analysis with a limited number of patient- and clinical variables and with CTA outcome was performed. No significant associations were found. However, the total number of patients in our analysis is small, thus limiting the possibilities for robust analysis between the two groups. Descriptive analysis of differences in evaluation of screening mostly showed similar results for patients with or without abnormalities on CTA as did satisfaction with various aspects of the screening. However, patients with abnormal CTA scans did report the emphasis placed on late effects as being burdening more often than patients without abnormalities. They also reported to be more nervous about the test results. Since the second set of questionnaires were sent out after patients finished the screening program and possible subsequent interventions, answers to both these questions could have been influenced by the result of the tests.

The role of cardiac screening in patients treated for HL is unclear. Previous screening studies have shown that prevalence of CAD detected by CTA in HL survivors is high (11, 12). Our phase II screening study did not only show a high prevalence of abnormalities on CTA in asymptomatic patients, but majority of these patients also underwent subsequent interventions.

Screening might be advisable, provided that a treatment improving outcome is available for patients with screen-detected abnormalities. Survival benefit of cardiac interventions has been demonstrated in high risk symptomatic cardiac patients (24). Whether a similar benefit can be achieved in asymptomatic HL survivors is as yet unknown. Aspects of screening such as cost-effectiveness, patient compliance and perceived burden and benefits of screening are of critical importance. Our analysis showed that the psychological impact of confrontation with possible late treatment sequelae does not seem to impede willingness to participate in screening, nor does it seem to influence satisfaction with participation.

In conclusion, in addition to a high prevalence rate of cardiac abnormalities and subsequent interventions in asymptomatic HL survivors after mediastinal radiotherapy, we have shown that the perceived burden and benefits result in a favourable patient evaluation of screening. Moreover, extensive counseling and comprehensive screening resulted in substantially increased information provision.

A positive effect of screening should be confirmed in a larger scale study. However, whether it proves to indicated or not, screening by means of CTA and subsequent cardiac intervention is highly valued and not considered an extra psychological burden.

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Appendix: Evaluation of screening questionnaire

The following questions specifically address your visit to the Cardiology Outpatient Clinic and the CT-scan that was performed. Please answer the questions by circling the number that best applies to you. There are no 'right' or 'wrong' answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quit a bit	Very much
1) How burdensome was the visit to the Cardiology outpatient clinic for you?	1	2	3	4
2) How burdensome was it for you to undergo the CT scan?	1	2	3	4
3) How nervous were you about receiving the test results?	1	2	3	4
4) How distressing is the emphasis that is placed on possible late side effects of your treatment to you?	1	2	3	4
How satisfied are you with:	**Not at all**	**A little**	**Quit a bit**	**Very much**
5) the information that was given to you concerning the purpose of this screening study?	1	2	3	4
6) the explanation given to you concerning the practical affairs of this screening study?	1	2	3	4
7) the explanation given to you concerning all test results?	1	2	3	4
8) the follow-up care after finishing all tests?	1	2	3	4
9) participating in this study?	1	2	3	4

chapter 5

Persisting fatigue in Hodgkin lymphoma survivors: A systematic review

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Abstract

Purpose
Hodgkin lymphoma (HL) survivors are at risk for adverse psychosocial events as a result from cancer diagnosis and treatment. Fatigue is one of the most frequently reported long-term symptoms and is often reported to interfere with daily life. We conducted a systematic review to determine prevalence, severity and predisposing factors of fatigue in HL survivors.

Methods
A literature search was conducted up to August 2012. Twenty-two articles comparing HL survivors with norm population data met all predefined selection criteria. Prevalence rates, levels of fatigue and clinical relevance of the results were determined.

Results
Prevalence of fatigue ranged from 11%-76% in HL survivors compared with 10% in the general population. Mean fatigue scores were 5-13% higher compared with the normative population; these findings were clinically relevant in 7 out of 11 studies. Increasing age was associated with higher levels of fatigue in HL survivors. Treatment modality and stage of initial disease were not associated with higher fatigue levels, while comorbidities or other treatment sequelae seemed to impact on the levels of fatigue.

Conclusions
HL survivors are at serious risk for developing clinically relevant, long-term fatigue. The impact of patient- and treatment characteristics on risk of fatigue is limited. Focus for future research should shift to the role of late-treatment sequelae and psychological distress symptoms.

Introduction

Hodgkin lymphoma (HL) is a relatively rare form of cancer. HL mainly affects adolescents and young adults. Significant therapeutic improvements have resulted nowadays in a favorable prognosis with an overall 5-year cancer-specific survival rate of 80% (1). The combination of highest incidence at a young age and improved survival has, however, led to an increasing number of HL survivors, who remain at risk for long-term complications of their treatment. Many studies have focused on adverse physical effects of treatment, such as an increased risk of secondary tumors (2, 3) or cardiovascular events (4, 5). Since the 1990s, studies have increasingly been focused on psychosomatic and psychosocial aspects of treatment and on the burden of having survived cancer. Fatigue is one of the most frequently reported symptoms among (long-term) survivors of HL (6-9). It is a main component of the multidimensional concept of health-related quality of life (HRQL). Fatigue and associated symptoms such as lack of energy or loss of vitality are among the symptoms rated most often as interfering with daily life. It has been reported to have a significant impact on perceived HRQL, even more so than some specific physical symptoms like nausea or pain (10). Fatigue itself has therefore been addressed in several studies, either briefly when measuring general HRQL in HL survivors, or more explicitly in studies using specifically designed and validated fatigue questionnaires. Most of these articles have also investigated the relation of fatigue with patient- and treatment-related factors. Since many of these studies were cross-sectional by design, their findings merely give an indication of possible associations, and their findings were often contradictory.

The purpose of this review was to provide a comprehensive overview of studies which have investigated fatigue in HL survivors, focusing on the prevalence and severity of fatigue and on associations between patient- and treatment-related factors and levels of fatigue.

Methods

Literature search strategy

A literature search was performed for all articles up to August 2012 using the electronic databases of Web of Science, PubMed en PsychINFO. Key terms used in the search were 'Hodgkin', 'Hodgkin's' and 'Hodgkins' in combination with '(Health related) Quality of Life', 'Value of Life', 'Fatigue', 'Energy Level' or 'Vitality'. Lists of references were verified to find additional publications that were not found by the computerized search.

Selection criteria

The literature search resulted in 1975 hits, of which 432 were duplicates. A total of 1395 were excluded based on title. Of the 148 abstracts retrieved, 52 were selected for full text review. Selection of articles was based on English language and measurement of fatigue by generic and/or fatigue-specific questionnaires. Abstracts, studies conducted before 1990, studies combining results of more than one type of tumor, or addressing fatigue in a specific subgroup of patients such as those who had intensified treatment for relapsed or refractory HL, were excluded. Subject of the studies had to be either comparison of fatigue in HL survivors with a well-defined norm population, and/or analysis of the relationship of fatigue with patient- and treatment characteristics. Specific focus was placed on the relationship between late-treatment sequelae or comorbid conditions and fatigue.

A total of 28 articles met the described selection. Six (11-16) review articles were further excluded since they only briefly discussed fatigue, and did not contain any additional studies to the remaining 22 original articles.

Quality assessment

The methodological quality of the selected articles was defined by scoring items from a standardized checklist with predefined criteria. These criteria originated from an established criteria list for systematic reviews that was previously used (16-18) which was slightly adapted for the purpose of this review. The criteria are listed in Table 5.1. For every one of the criteria that was met, one point was assigned to the study. In case of absence of an item, zero points were assigned. Therefore, a total number ranging from 0 to 14 points per study was assigned to each study. A higher total score indicates a higher quality assessment. Studies scoring 75% ($\geq$11 points) or more were considered as 'high quality studies'. A score between 50% and 75% was considered to be moderate and studies scoring less than 50% were qualified as 'low quality'.

The evaluation of the methodological quality of studies was done separately by LAD and SO. A consensus meeting was held to discuss differences between the two reviewers and a consensus score was assigned.

To determine clinical relevance of reported differences in mean fatigue scores for studies comparing HL survivors to a norm or control group we used the following guidelines. For the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) differences were defined according to the EORTC guidelines as trivial (0-5 point difference), small (5-13 point difference) or medium (13-19 point difference) (19). Concerning the Short Form-36 (SF-36) $\geq$ 3

Table 5.1: Criteria for assessing the methodological quality of studies of fatigue in HL survivors*

Quality of life assessment	
1.	a validated fatigue specific or generic HRQL questionnaire measuring fatigue or vitality is used (*e.g.* FQ, SF-36, EORTC QLQ-C30)
Study population	
2.	a description is given of at least two socio-demographic variables
3.	a description is given of at least two clinical variables
4.	in- and exclusion criteria are described
5.	response rate to the QoL or fatigue questionnaire is $\geq$ 65%
6.	information is provided on differences of characteristics between responders and non-responders
7.	time since diagnosis is provided
Study design	
8.	the study size consist of at least 50 participants
9.	data are prospectively gathered
10.	the process of data collection is described
11.	missing data are described
Results	
12.	the results are compared between two groups or more (*e.g.* healthy population, groups with different treatment or age and/or compared with at least two time points)
13.	mean, median, standard deviations or percentages are reported for the most important clinical outcome measure
14.	statistical proof for the findings is reported

* adapted from (16-18).

Abbreviations: HRQL = health-related quality of life; FQ = Fatigue questionnaire; SF-36 = short form 36; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire.

points difference was considered clinically relevant (20). For the other questionnaires, Norman's 'rule of thumb' was used, whereas a difference of $>$ 0.5 SD indicates a discriminating change in fatigue scores (21).

Results

Study characteristics

All 22 identified studies had been published between 1993 and 2013. Seven studies focused specifically on fatigue (22-28); while in the other 15 fatigue was measured and reported as part of the assessment of HRQL (8, 9, 29-41).

Two studies had a prospective, longitudinal design (8, 39). Both of these studies were HRQL protocols associated with large multicentre clinical randomized trials, comparing different treatment strategies. Eighteen studies had a cross-sectional design, either in a single center (23, 25-27, 29, 30, 33, 35-38, 40, 41) or multicenter setting (9, 24, 31, 32, 34). Two studies were follow-up studies of earlier cross-sectional reports (22, 28).

In 12 of the 18 cross-sectional studies, HL survivor fatigue levels were compared with data from a general norm population (22, 24, 25, 29-31, 34, 37) or to matched cases (9, 23, 35, 36). The remaining six described fatigue within a HL survivor cohort and were selected because they explored associations between fatigue and patient- or treatment parameters. The total number of patients included in all studies ranged from 42 (41) to 935 (39), and median time since diagnosis ranged from 6 months (8) to 24 years (28).

Of all 22 studies, 16 reported on associations of clinical and/or treatment characteristics with higher levels of fatigue (8, 9, 22-27, 29-31, 35, 38-41).

The validated questionnaires that were used in the studies either measured fatigue specifically (Fatigue questionnaire (FQ) (42), Multidimensional Fatigue Inventory (43)), (22, 24, 25, 29, 39), or measured fatigue as a scale of a generic or cancer-specific HRQL questionnaire (Short Form 36 (SF-36) (44), EORTC QLQ-C30 (45)), (8, 23, 24, 28, 30, 31, 34-39, 41). The SF-36 addresses fatigue and energy by measuring a four-item vitality scale, the EORTC QLQ-C30 measures a separate three-item fatigue scale. Questionnaires less often used were the Profile of Mood States (POMS(46)), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F (47)) and the Schedule for the Evaluation of Individual QoL-Direct Weighting (SeisQoL-DW (48)), each used in one study (9,23, 32).

Prevalence of fatigue

Seven studies reported prevalence rates of fatigue, ranging between 11% and 76% (see Tables 5.2 and 5.3). However, five of these seven studies reported on the same Norwegian HL survivor cohort, measured at two time intervals. As a result, they reported similar fatigue prevalence rates, defined as a dichotomized score of 4 out of 11 questions in the FQ, of 26% (measured in 1994, (25-27)) and 30% (measured in 2002, (29, 33)). Rates of fatigue in the HL survivor cohort (26-30%) in these five studies were significantly higher than the 10% fatigue that was measured in the population survey (25, 29, 49).

Two studies reported on other cohorts of HL survivors. One (40) reported a prevalence of at least some level of fatigue in 76% of 168 HL survivors, using a score of $\geq$ 20 out of a possible 100 in the EORTC QLQ-C30 as cut-off. The other (32) found that 11% of 121 HL survivors self-indicated fatigue as an area importantly affected by HL diagnosis and treatment.

Fatigue scores

Sixteen studies reported mean fatigue scores in HL survivors (see Tables 5.2 and 5.3). Among the 12 studies that compared mean fatigue scores to a norm population or a set of matched cases, the two smallest case-control studies did not find significant differences in levels of fatigue (35, 36). The remaining 10 studies all showed statistically significant higher fatigue scores in HL survivors compared with norm data (9, 22-25, 29-31, 34, 37). Only two of these studies addressed the clinical relevance of higher fatigue scores in HL survivors by reporting effect size. Hjermstad *et al.* (29) reported an effect size of 0.7 measured by FQ, which was defined as moderate, and Loge *et al.* reported a small effect size of 0.23 measured by SF-36 (30). Overall, differences in fatigue scores between HL survivors and normative populations ranged from 5-13%. Three studies used the EORTC QLQ-C30 questionnaire, of which two measured a difference of 6.5 points (6.5%), compared with the general population (24, 34). Brandt *et al.* (37) found a difference of 13 points (13%) in fatigue scores on the QLQ-C30 between HL patients treated with chemotherapy alone, and a German reference population. Two studies reported on vitality scores using the SF-36, and found differences of 5% and 8%, respectively (30, 31). Three studies used the FQ for assessment of fatigue. All of these studied the same HL cohort (at two different time intervals) and used a general practitioner survey for norm data, and reported differences in fatigue scores of 6-7% (22, 25, 29).

The two prospective, longitudinal studies evaluating fatigue in HL trial cohorts (8,

Table 5.2: Overview of studies of fatigue in HL survivors without comparison to normative data

Study, year	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm popu-lation	Fatigue outcome	Major findings	Quality Score
Ganz (8) 2003	247	33 (17-85)	0.5, 1 and 2	RT or CMT	Longitudinal prospective	98-70%	SF-36	No	Increase of fatigue first 6 months after treatment, returning to baseline level at one year after diagnosis	Fatigue more severe after CMT, both treatment arms return to baseline level of fatigue	14
Heutte (39) 2009	935	NR (15-70)	7.5 (4.3-9.8)	RT or CMT	Longitudinal prospective	74-32%	EORTC QLQ-C30 MFI	No	Improvement of fatigue up to two years after treatment in 65% of patients, no baseline reports.	Increasing fatigue with age. Fatigue at end of treatment only predictor for persistent fatigue	14
Loge (26) 2000 *	421	NR	3-23	RT, CT or CMT	Cross-sectional	92%	FQ	No	Prevalence of fatigue 26%mean fatigue score not reported	Higher fatigue levels with age and lower educational level. No differences between: stage, gender, treatment or time since diagnosis	13
Knobel (27) 2001 *	92	37 (30-43)	9 (6-12)	RT or CMT	Cross-sectional	n.a.	FQ	No	Mean fatigue score 15, physical 10, mental 5. Prevalence of fatigue 26%	More fatigue in patients with pulmonary dysfunction. No association with cardiac or thyroid disease or patient and treatment characteristics	12
Norum (41) 1996	42	NR	4.3 (16-120)	RT, CT or CMT	Cross-sectional	86%	EORTC QLQ-C30	No	Mean fatigue score 28.6	Higher fatigue scores in menNo differences between treatment	11
Ng (27) 2013	422	52 (31-78)	24 (14-43)	RT, CT or CMT	FU on cross-sectional study	65%	FACIT-FSF-36	No	Overall no significant difference in fatigue scores compared with earlier	Significant increase of fatigue in patients suffering from cardiac or pulmonary complications	11
Greill (38) 1999	126	NR	9.1 SD ± 7.0	RT, CT or CMT	Cross-sectional	65%	EORTC QLQ-C30	No	Mean fatigue score not reported	More fatigue after CMT versus CT or RT alone	10
Miltenyi (40) 2010	168	43 (18-77)	9.5 (0-36)	RT, CT or CMT	Cross-sectional	NR	EORTC QLQ-C30	No	Any form of fatigue 76%	More fatigue in patients suffering from late complications and those more than 20 years after treatmentNo differences between stage, treatment, gender, B-symptoms	9

Abbreviations: HL = Hodgkin lymphoma; n.a: .not applicable; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; SF-36 = short-form 36; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MFI= Multidimensional Fatigue Inventory; FQ= fatigue questionnaire.

* Studies reporting results from the same HL survivor cohort. NR: not reported.

Table 5.3: Overview of studies on fatigue in HL survivors with comparison to normative data

Study	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm population	Fatigue outcome	Major findings	Clinically relevant difference	Quality Score
Hjermstad (22) 2005 *	476	46 (21-74)	16 (4.4-36)	RT, CT or CMT	FU on cross-sectional study	81%	FQ	Yes, comparison to age, sex and education adjusted GP survey	Moderately higher total fatigue in HL survivors	Increasing fatigue with age. Increased persisting fatigue in patients presenting with B-symptoms	No	13
Hjermstad (29) 2006 *	476	46 (21-74)	16 (4.4-36)	RT, CT or CMT	Cross-sectional	81%	SF-36 FQ	Yes, comparison to age, sex and education adjusted GP survey	3 times more chronic fatigue HL survivors than norm population (30% vs 11%)	No differences between: time since diagnosis, stage, treatment (intensity), B-symptoms	No	13
Loge (30) 1999 *	459	44 (40-49)	12.2 (3 -23)	RT, CT or CMT	Cross-sectional	82%	SF-36	Yes, comparison representative sample of Norwegian population (N=3500)	Vitality significantly lower in HL survivors	No significant differences in fatigue between treatment, stage, relapse, time since diagnosis	Yes	13
Loge (25) 1999 (JCO) *	459	44 (40-49)	12.2 (3-23)	RT, CT or CMT	Cross-sectional	82%	FQ	Yes, comparison representative sample of Norwegian population (N=3500)	Prevalence of fatigue 26% vs 11%, higher fatigue scores in HL survivors	Higher fatigue with age and low educational level. No differences between: stage, treatment, time since diagnosis, gender	-	13
Mols (31) 2006	132	NR	5- 15	RT, CT or CMT	Cross-sectional	80%	SF-36, QLQ-CS	Yes, comparison to a Dutch age matched norm population	Lower vitality scores in HL survivors	More fatigue in 5-10 yr survivors than in norm population. Differences disappear after more than 10 yrs after treatment	Yes	12
Oldervoll (33) 2007 *	476	46 (21-73)	15.7-17 SD 89.5 and 82.6	RT, CT or CMT	Cross-sectional	81%	FQ	Yes, results partly compared to epresentative sample of Norwegian population	Prevalence of chronic fatigue HL survivors 30%, no comparison fatigue level to norm data	-	-	12
Rüffer (24) 2003	836	NR	5.2	RT, CT or CMT	Cross-sectional	61%	QLQ-C30 MFI	Yes, comparison to 935 age, gender and living area matched healthy controls	Higher fatigue in HL survivors, both QLQ C30 and MFI measured	Increasing fatigue with age, KPS, relapse, B-symptoms. No differences between: gender, treatment, stage	Small	12

Abbreviations: HL = Hodgkin lymphoma; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; POMS = Profile of Mood States; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; FQ = fatigue questionnaire; SF-36 = short-form 36; Facit-F = Functional Assessment of Chronic Illness Therapy-Fatigue; MFI = Multidimensional Fatigue Inventory; SeisQoL DW = Schedule for the Evaluation of Individual QoL-Direct Weighting.

* Studies reporting results from the same HL survivor cohort and norm population.

Table 5.3: Overview of studies on fatigue in HL survivors with comparison to normative data (continued)

Study	No of HL survivors	Mean age at time of study (yrs, range)	Mean time since diagnosis (yrs, range)	Treatment	Design of study	Response rate	Fatigue measure-ment	Norm population	Fatigue outcome	Major findings	Clinically relevant difference	Quality Score
Bloom (9) 1993	85	32.2	3.1	RT or CMT	Cross-sectional	NR	POMS	Yes, comparison to testis carcinoma patients, gender matched	More fatigue and less return of energy in HL survivors compared with testis carcinoma patients	-	No	11
Joly (34) 1996	93	42 (23-85)	10 (4-17)	RT, CT or CMT	Cross-sectional	90%	EORTC QLQ-C30	Yes, comparison to 183 age, gender and city of residence matched healthy controls	Mean fatigue score significantly higher in HL survivors	-	Small	11
Ng (23) 2005	511	44 (16-82)	15 (5-32)	RT, CT or CMT	Cross-sectional	60%	FACIT-FSF-36	Yes, comparison to siblings of HL patients	Fatigue borderline significantly higher in HL survivors compared with siblings. Prevalence fatigue 37% HL survivors vs 27%.	Higher levels of fatigue in case of cardiac disease. No differences between gender, age, treatment or thyroid disease	No	11
Tulder (34) 1994	81	47 (25-77)	14 (10-18)	RT or CMT	Cross-sectional	92%	SF-36	Yes, comparison to hospital visitors, age and gender matched	Vitality HL survivors not significantly lower	-	Yes	11
Wettergren (32) 2003	121	47 SD 11.9	14 SD 64.9	RT, CT or CMT	Cross-sectional	62%	SeisQoL DW	Yes, results partly compared to random sample of 236 Swedish citizens	10% HL survivors mentioned fatigue, no comparison of fatigue to norm data	-	-	11
Brandt (37) 2010	98	NR (21-72)	3.5 and 11	HD-CT + SCT or CCT	Cross-sectional	64%	EORTC QLQ-C30	Yes, comparison to healthy German reference population	Fatigue significantly higher in both groups of HL survivors compared with norm	-	Medium	10
Gil (35) 2003	46	43 (15-80)	7.6 (0.8-22.1)	RT, CT or CMT	Cross-sectional	69%	EORTC QLQ-C30	Yes, comparison to 46 healthy individuals from medical faculty	Fatigue not significantly higher in HL survivors	No differences in fatigue between treatment	Small	10

Abbreviations: HL = Hodgkin lymphoma; RT = radiotherapy; CT = chemotherapy; CMT = combined modality treatment; SCT = stem cell transplantation; HD-CT = high dose chemotherapy; CCT = conventional chemotherapy; POMS = Profile of Mood States; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; FQ = fatigue questionnaire; SF-36 = short-form 36; Facit-F = Functional Assessment of Chronic Illness Therapy-Fatigue; MFI = Multidimensional Fatigue Inventory; SeisQoL DW = Schedule for the Evaluation of Individual QoL-Direct Weighting.

Table 5.4: Association of patient, clinical and treatment characteristics with observed fatigue

Variable	No. of studies with positive relation / total no of studies investigating variable	No. of subjects with positive relation / total no of subjects in studies investigating variable	Type of relation
Age*	4 / 7	2332 / 3255	Increasing fatigue with older age
Sex*	2 / 7	977 / 3212	935 female more fatigue, 42 male more fatigue
Education*	1 / 2	459 / 970	More fatigue in lower educated
Systemic symptoms*	2 / 5	1771 / 2891	More fatigue if systemic symptoms present at diagnosis
Stage*	0 / 5	0 / 2200	No influence of stage on fatigue
Treatment*	2 / 11	380 / 3955	More fatigue after combined modality treatment
Time since diagnosis*	4 / 7	1479 / 2942	1311 decrease of fatigue over time, 168 increase of fatigue over time
Relapse*	1 / 4	836 / 1991	More fatigue after (treatment for) relapse
Smoking	1 / 2	511 / 1347	More fatigue in smokers
Psychiatry	2 / 2	932 / 932	More fatigue in patient with psychiatric comorbidity
Late complications	3 / 3	771 / 771	More fatigue in presence of late complications/comorbidity

* exclusion of overlapping results from studies reporting on the same HL cohort

39) did not report precise levels of fatigue, but reported on the course of fatigue over time, both showing decreasing fatigue over time after completion of treatment. Ganz *et al.* (8) showed a decrease of fatigue from 6 months after diagnosis, with fatigue levels returning to baseline level at two years after diagnosis.

Socio-demographic, clinical and treatment characteristics associated with fatigue

Among the 22 studies, 17 studied fatigue in relation to socio-demographic, clinical, or treatment-related characteristics. An overview of these characteristics and their association with fatigue is presented in Table 5.4. Overlapping results from studies reporting from the same HL cohort were excluded. Variables that were most frequently associated with fatigue were gender, age, stage of HL, treatment, time since diagnosis and occurrence of relapse (8, 9, 22-27, 29-31, 35, 38-41).

Seven studies examined the association of gender and levels of fatigue. Five studies found no relationship (8, 22-24, 40), while one large longitudinal study showed that women had statistically significant worse scores of fatigue as measured by EORTC QLQ-C30 and general fatigue as measured by the MFI, but failed to show a

relation between gender and the other fatigue dimensions of the MFI (39). In contrast, in a study of 42 HL survivors Norum *et al.* found that men had worse outcomes in fatigue scores than women (41).

Four out of seven studies found significantly higher fatigue levels in older patients (9, 22, 24, 39), while three other studies did not confirm this (8, 23, 40). None of the five studies relating initial stage of HL to levels of fatigue found a significant association (8, 22, 24, 26, 29, 40).

Eleven studies have investigated fatigue levels with different treatment strategies, such as radiotherapy versus chemotherapy or combined modality treatment. Nine of these studies, all cross-sectional in design, did not find any relationship (9, 22-24, 29, 35, 39-41). One longitudinal study did report higher fatigue levels with combined modality treatment 6 months after diagnosis when compared with radiotherapy alone, but differences between treatment arms disappeared over a longer time period and were most likely related to differences in duration between the two treatment arms (8). One cross-sectional study found higher fatigue scores after combined modality treatment when compared with chemotherapy or radiotherapy alone (38).

Time since diagnosis was examined in 7 studies. In four studies, time since diagnosis was associated with fatigue; one cross-sectional study showed higher fatigue prevalence rates over time (40) while 2 longitudinal studies and 1 cross-sectional study showed decrease of fatigue over time (8, 31, 39). Three studies did not find any relation between time since diagnosis and fatigue (22, 23, 29).

Three out of four studies did not find an association between occurrence of relapse and fatigue (22, 23, 40). One found higher levels of fatigue after relapse of disease (24). Other parameters, such as level of education or smoking were less frequently investigated and mostly showed conflicting results.

Conflicting data concerning variables associated with fatigue could not be explained by differences in length of follow-up duration or instruments used.

Late treatment sequelae or comorbidities and fatigue

Three cross-sectional studies focused specifically on the impact of late-treatment sequelae or comorbid conditions on levels of fatigue (23, 27, 40). Ng *et al.* compared 511 HL survivors with 224 siblings (23). They observed a modest difference in mean fatigue scores measured by the FACIT-F, and in multivariate analysis found a significant positive correlation of cardiac disease with fatigue. They did not find an association between adequately suppleted hypothyroidism and fatigue. In their 2013 follow-up study among the HL survivors, they showed a statistically significant worsening of fatigue over time, in those patients suffering from late cardiac or pulmonary

complications (28). Knobel *et al.* (27) found higher levels of fatigue in 92 HL survivors suffering of pulmonary dysfunction, and confirmed absence of higher levels of fatigue in survivors with treated hypothyroidism. However, they did not find an association between fatigue and cardiac disease.

Miltenyi *et al.* (40) found higher fatigue levels in HL survivors with late treatment complications in general.

Discussion

This systematic review, including 22 large studies that investigated prevalence of fatigue or fatigue levels in HL survivors, showed prevalence rates of 11-76% in HL survivors, compared with 10% in the general population. We also found 5-13% higher levels of fatigue in HL survivors when compared with the general population; differences that were mostly clinically relevant. There was some evidence that older age at diagnosis might lead to higher fatigue levels. Treatment modality and stage of initial HL did not seem to be associated with fatigue levels. Evidence for the influence of characteristics such as level of education, time since diagnosis, or relapse of disease was often contradictory.

Although HL is a relatively rare disease, its occurrence at a young age and the increasing numbers of long-term survivors reporting long-lasting fatigue and reduced vitality have prompted specific studies of fatigue among HL survivors. For 19 of the 22 included studies, (8, 9, 22-34, 36, 38, 39, 41) quality assessment scores ranged from 11 to 14, indicating a high methodological quality. Shortcomings were mostly lack of description of missing data (N=12) and lack of description of non-responders (N=6). The latter makes it more difficult to estimate potential selection bias. Another frequent shortcoming was lack of a prospective design (N=20).

The majority of the studies were cross-sectional by design, which makes them suitable for evaluating prevalence rates of fatigue, but limits the possibility to evaluate causal relationships between prognostic factors and fatigue. Reported associations were often contradictory, with the exception of the consistent finding that initial stage of HL did not impact fatigue rates.

Only two studies had a prospective, longitudinal design. Both studies showed a decrease in levels of fatigue over time. Ganz *et al.* (8) showed that fatigue levels in both treatment arms, measured by the SF-36, returned to baseline levels measured before start of treatment. These baseline levels, however, were lower than population fatigue levels measured by SF-36 in other cross-sectional studies (30, 31, 36), both in

HL survivors and in norm populations. This could be due to a patient selection bias, since the study accompanied a randomized trial on efficacy of different treatment strategies.

Concerning influence of treatment modalities on reported fatigue in these longitudinal studies, one study did not find different levels of fatigue between the two different treatment arms, while the other did. This may be due to the fact that fatigue was measured at a fixed time point of 6 months after diagnosis, without accounting for the difference in treatment duration between the radiotherapy alone group and the combined modality group. Twelve of the 13 cross-sectional studies addressing treatment modalities found no association with levels of fatigue. Although treatment modality may not have a direct impact on the risk of chronic fatigue, late treatment sequelae may. Research on associations between fatigue and comorbidities or late treatment complications is limited. A relation was suggested in three cross-sectional studies. However, only one of these studies compared the results for HL survivors with comorbidities to matched case controls. Levels of fatigue may also be negatively influenced by the presence of depression, since presenting symptoms may overlap between these conditions. There was only one study that combined measurement of fatigue and depression in a group of 457 HL survivors and found significant overlap (26).

When we limit the evaluation of prognostic factors to the studies with the highest quality scores (8, 22, 24, 25, 27, 29, 31, 39), influence of patient and treatment characteristics on levels of fatigue seems to be limited to increasing age.

Definition of fatigue is difficult and often subjective. Therefore, measurement of fatigue varies greatly between studies. It is often addressed through a variety questionnaires. It is unclear how these questionnaires correlate and if they would identify the same fatigue cases. Also, the interpretation of differences in fatigue scores between patients and norm populations remains difficult. Statistically significant differences do not necessarily imply clinical relevance. It was possible to determine clinical relevance of reported differences in fatigue levels between HL and population controls for 11 studies, of which 7 confirmed a clinically relevant higher fatigue score in HL survivors. These findings are in line with clinical practice, where a majority of the HL survivors report to suffer from the effects of chronic fatigue in their daily lives, while lack of clear predisposing factors limit treatment options. Optimal treatment of comorbidities and especially of anxiety and depression might be of benefit.

In conclusion, HL survivors are at serious risk for developing chronic fatigue and loss of vitality, since all except the two smallest studies showed 15-20% higher prevalence rates of fatigue compared with population controls. Most studies showed clinically relevant differences. Solid evidence for the influence of prognostic factors on fatigue is limited; gender, initial stage of disease and treatment modality do not

seem to play an important role in the development of chronic fatigue. To be able to provide a clinically meaningful treatment option for the chronic fatigue in HL survivors, focus should switch to the role of comorbidities, late treatment sequelae and the influence of psychological distress on developing fatigue in long-term HL survivors, preferably by assessing longitudinal data on HL survivors compared with a matched norm population.

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chapter 6

Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity

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Abstract

Purpose
Fatigue is a frequent and persistent problem among Hodgkin lymphoma (HL) survivors. We investigated the prevalence of clinically relevant fatigue in HL survivors and the relation between fatigue and anxiety and depression.

Methods
Fatigue was measured through the generic European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and Fatigue Assessment Scale (FAS). Anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS). Questionnaires were mailed to 267 HL survivors. Results were compared with a Dutch age-matched normative population.

Results
Response rate was 68% (median age 46 years, mean time since diagnosis 4.6 years). Prevalence of fatigue was significantly higher among HL survivors than in the norm population (FAS 41% *vs* 23%, QLQ-C30 43% *vs* 28%), as were fatigue levels. There was a significant association between fatigue, anxiety and depression. Of the HL survivors with high symptom levels of depression, 97% also reported fatigue. In multivariate analysis, depression was strongly associated with high levels of fatigue and, to a lesser extent, anxiety and comorbidity.

Conclusions
Prevalence rates of fatigue are significantly higher in HL survivors than in the general population and differences are clinically relevant. Depression and anxiety were strongly associated with high levels of fatigue. Reducing fatigue levels by treatment of depression and anxiety should be further explored.

Introduction

Over the past decades, survival of Hodgkin lymphoma (HL) patients has improved dramatically with 5-year overall survival rates ranging from 90% to 95% (1, 2). This has mainly been due to the introduction of multi-agent chemotherapy and improved radiotherapy techniques. However, with improved life expectancy, patients often face long-term effects caused by their treatment, such as treatment-induced secondary tumors or cardiovascular disease (3-6).

Apart from these adverse physical effects, many HL survivors also report suffering from long-term psychosomatic and psychosocial problems (7-10). A number of studies have focused on these psychosocial issues in HL survivors, mainly addressing overall health-related quality of life (HRQL). A recent review of HRQL in HL survivors showed persistent problems in physical, role-physical, social and cognitive functioning (11). These problems were most prevalent in HL patients treated with combined modality treatment, in women and in patients of older age. Furthermore, a number of studies have focused specifically on fatigue, because this is one of the most frequently reported and most persisting symptoms in HL survivors, and has consistently been reported to have significant impact on HRQL (7, 12-16). The mechanism that causes fatigue is largely unknown. Associations between fatigue and clinical or patient characteristics have been made, mainly focusing on the influence of treatment, time since diagnosis and age. However, such studies have provided conflicting results (7, 15-18). The impact of comorbid conditions, whether or not caused by cancer treatment, on perceived fatigue has been studied less frequently. All conducted studies reported increased fatigue in HL survivors with comorbidities (18-20). Of these studies, only Ng *et al.* compared their results with a norm population consisting of a group of siblings. Fatigue in the HL survivors was more frequent and was associated with the presence of cardiac disease.

Fatigue is reported to be a frequent symptom of depression. Few studies have explored the relationship between fatigue and depression in HL survivors. Loge *et al.* reported increased levels of psychological distress in nearly 50% of fatigued HL survivors; however, no comparison with a norm population was made (8). Ng *et al.* found that having a psychiatric condition was a significant variable for increased fatigue (18). Because of high prevalence rates of fatigue in the general population, results on fatigue surveys of cancer survivors should be interpreted with caution and be compared with an age- and sex- matched norm population.

The purpose of this study was to investigate the prevalence of clinically relevant fatigue in HL survivors in the Netherlands compared with an age- and sex-matched Dutch population, and to determine the relationship between fatigue and depression, and other comorbid conditions.

Methods

HL survivors

A cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR) among HL survivors. The ECR records data on all newly diagnosed cancers in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and 2 large radiotherapy institutes. The ECR was used to select all patients who were diagnosed with HL between January 1st 1999 and December 1st 2010. Deceased patients were excluded by linking the ECR database with the Central Bureau for Genealogy. Hodgkin lymphoma survivors were contacted by mail through their physicians and were asked to participate in this cross-sectional study by completing and returning a set of questionnaires. In May 2009, patients between 6 months and 10 years after diagnosis received the first questionnaire. In November 2009, patients diagnosed between May 2008 and May 2009 were invited to participate and in May 2011, patients diagnosed between May 2009 and December 2010 were invited. Ethical approval for this study was obtained from the University of Tilburg certified Medical Ethics Committee.

Questionnaires

Survivors of HL were asked to complete the validated Dutch version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ C-30). The QLQ-C30 measures cancer specific HRQL and contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, six single items assessing additional symptoms and three symptom scales (pain, fatigue and nausea/vomiting). For all items, Likert-type response scales are used, with total scores per item ranging from 4 to 7 points. All subscales and individual item responses are linearly converted to 0 - 100 scales (21). As a cutoff for fatigue caseness, we defined a score >23.9 for the EORTC QLQ-C30 although the fatigue symptom subscale has not been validated as a stand-alone measure for fatigue (23). For partially incomplete questionnaires imputation of the mean was used for scales containing at least 50% of the scores (22). Fatigue was also measured with the Fatigue Assessment Scale (FAS), a validated 10-item questionnaire reflecting mental and physical fatigue (24, 25). Total scores range from 10 to 50, with a higher score reflecting a higher level of fatigue. A score over 21 points indicates probable caseness of fatigue (25).

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS)(26, 27), which measures levels of symptoms of anxiety and depression in two subscales of seven items each. A score $>$ 8 on either subscale indicates a possible caseness for an anxiety or depressive disorder; a score $>$ 11 indicates a probable caseness. For the HADS a score $>$ 8 on either subscale was used as a cut-off value for defining caseness of anxiety or depression, as this score achieves an optimal balance between sensitivity and specificity (26-28).

Comorbidity was evaluated by the Self-administered Comorbidity Questionnaire (29). Education and marital status were also assessed in the questionnaire. Information on tumor and treatment characteristics was available from the ECR.

Norm population

The norm population was selected from a reference cohort of approximately 2200 individuals from the general Dutch population (CentER panel (30)). The set of questionnaires completed for this study included the QLQ-C30, FAS and HADS questionnaires and also data on socio-demographics and comorbid conditions were provided. To compare the results with that of the HL survivor cohort, we made an age- and sex-matched selection from this normative population. This reference cohort is representative for the Dutch-speaking population in the Netherlands (30, 31).

Statistical analysis

All statistical analyses were performed using SPSS version 20 (SPSS inc., Chicago, IL, USA). Patient, tumor and treatment characteristics between respondents, non-respondents and patients with unverifiable addresses were compared using t-test (numerical variables) and chi-square (categorical variables). A two-sided p-value $<$ 0.05 was considered statistically significant.

Differences between fatigue caseness from the EORTC QLQ-C30 and FAS and/or caseness of anxiety or depression from the HADS in HL survivors and the norm population, were calculated by chi-square tests.

Mean fatigue scores from the EORTC QLQ-C30 and FAS were compared between HL survivors and the norm population using independent sample t-tests. Clinical relevance of the differences was defined according to guidelines for the interpretation of the EORTC QLQ-C30 (23) and according to Norman's rule of thumb for the

FAS, indicating a ± 0.5 SD difference of the norm in scores as a discriminating change (32).

Multivariate logistic regression analyses using the dichotomous FAS score were performed to analyze the association of socio-demographic, tumor, treatment and comorbidity variables and fatigue. Variables were included into the model in separate steps. Demographic variables were added first, then clinical variables and, third, psychological distress. A two-sided p-value < 0.05 was considered statistically significant.

Results

Characteristics of the respondents and non-respondents

In total, 180 (68%) of the 267 HL survivors completed and returned the questionnaires. Missing items on the completed questionnaires were < than 3% (N=17). Responders were more often male and older than non-responders and than those with unverifiable addresses (Table 6.1). Mean time since diagnosis was 4.6 years; mean age at the time of survey among HL responders was 46 years and 55% had received combined modality treatment. Only 3% had been treated with radiotherapy alone. There were no statistically significant differences between HL responders and the norm population concerning marital status or education (Table 6.2). With regards to comorbidities, HL responders less often reported hypertension (9% *vs* 20%), but more often thyroid disease (9% *vs* 5%) and depression (11% *vs* 3%) than the norm population.

Fatigue prevalence and symptoms of anxiety and depression

There were significantly more persons with fatigue among the HL survivors compared with the norm population (Figure 6.1 and Table 6.3). The QLQ-C30 fatigue subscale identified a 43% prevalence of fatigue among the HL survivors, versus 28% in the norm population (p=0.002). The FAS questionnaire showed fatigue prevalence rates of 41 and of 23%, respectively (p<0.001). Identification of fatigue cases was consistent between the QLQ-C30 and the FAS questionnaire in 83% of the HL survivors and in 81% of the norm population. Among the HL patients, 23% had high symptom

Table 6.1: Patient and treatment characteristics of the HL survivor cohort

	HL responders		Non-responders		Unverifiable address		P-value
	N	%	N	%	N	%	
Total	180		35		52		
Age at time of survey in years							
Mean (SD)	46 (15.6)		40 (13.6)		40 (13.9)		*p*=0.01
Range	19-84		21-79		20-83		
< 40	75	41	18	51	34	65	*p*=0.02
40-60	70	39	14	40	14	27	
> 60	35	19	3	9	4	8	
Time since diagnosis in years							
Mean (SD)	4.6 (2.9)		5.9 (3.2)		4.6 (3.0)		*p*=0.07
< 5	102	57	14	40	29	56	*p*=0.11
5 - 10	76	42	19	54	23	44	
> 10	2	1	2	6	0		
Sex							*p*=0.06
Male	99	55	23	66	37	72	
Female	81	45	12	34	14	28	
Stage at diagnosis							*p*=0.60
I	31	17	7	20	9	17	
II	94	52	14	40	19	37	
III	26	15	6	17	12	23	
IV	18	10	4	12	6	12	
Treatment							*p*=0.50
RT	6	3	0		1	2	
CT	74	41	18	51	25	48	
RT + CT	99	55	16	46	23	44	

Abbreviations: HL = Hodgkin lymphoma; RT = radiotherapy only; CT = chemotherapy only; RT + CT= radiotherapy and chemotherapy.

Table 6.2: Characteristics of the study participants

	HL responders		Norm population		P-value
	N	%	N	%	
Total	180		327		
Age at survey in years					
Mean (SD)	46.1 (15.6)		48.8 (15.7)		p=0.90
Range	19-84		20-85		
$<$ 40	75	42	117	36	p=0.28
40-60	70	39	129	39	
$>$ 60	35	19	81	25	
Sex					p=0.43
Male	99	55	168	51	
Female	81	45	159	49	
Self-reported comorbidity					
Cardiac	17	9.4	21	6.4	p=0.07
Stroke	2	1.1	1	0.3	p=0.16
Hypertension	16	8.9	65	19.9	p=0.01
COPD	19	10.6	41	12.5	P=0.92
Diabetes Mellitus	8	4.4	25	7.6	p=0.39
Anemia	4	2.2	14	4.3	p=0.44
Thyroid disease	17	9.4	16	4.9	p=0.008
Depression	19	10.6	11	3.4	$p<0.001$
Comorbidity conditions					p=0.37
No comorbidity	87	48	149	46	
$\leq$ 2 comorbidities	63	35	134	41	
$>$2 comorbidities	21	12	44	13	
Marital status					p=0.62
Partner	133	74	252	77	
No partner	44	24	75	23	
Education level					p=0.10
Low	14	8	13	4	
Medium	107	59	191	58	
High	56	31	122	37	

Abbreviations: COPD = chronic obstructive pulmonary disease; HL = Hodgkin lymphoma.

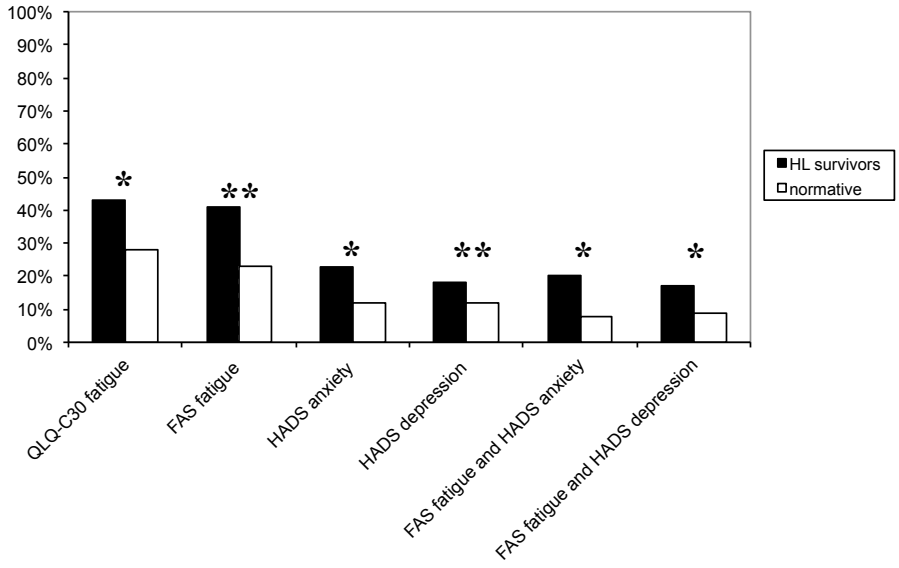

Figure 6.1: Prevalence of caseness of fatigue according to fatigue subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QlQ-C30) and fatigue assessment scale (FAS), and caseness of anxiety or depression according to the Hospital Anxiety and Depression Scale (HADS) for both Hodgkin lymphoma survivors and the age- matched Dutch population. The two last columns describe the prevalence of combined fatigue and anxiety or depression among all HL survivors and of the norm population. * $P < 0.05$; ** $P < 0.01$.

levels of anxiety and 18% of depression, compared with 13% and 12% in the norm population.

Of all responding HL survivors, 20% were identified both as a fatigue case and an anxiety case; 17% were both fatigued and had symptoms of depression. These numbers were significantly lower in the norm population (8%, $p<0.001$ and 9%, $p=0.004$ respectively, Figure 6.1). The prevalence of fatigue among HL survivors with a high symptom level of depression was 97%, compared with 76% in the norm population.

Similar relationships were found for cognitive functioning (impairment of concentration and memory) and fatigue, with significantly lower social functioning and especially lower cognitive functioning among HL survivors compared with the norm population (see Table 6.3). There was a clear association between fatigue and cognitive impairment. The mean scores of cognitive function were lower among fatigued

Table 6.3: QLQ-C30, FAS and HADS mean scores for HL survivors vs norm population

	HL		Norm		P-value	Clinical relevance (23, 32)
	Mean	SD	Mean	SD		
QLQ C30						
Functional scales						
Role functioning	83.8	24.4	89.6	20.0	p=0.05	Trivial
Physical functioning	87.1	15.7	90.9	14.8	p=0.08	Trivial
Cognitive functioning	82.5	22.0	92.5	15.7	$p<0.001$	Medium
Emotional functioning	82.4	22.9	87.9	17.8	p=0.03	Small
Social functioning	86.4	22.2	92.8	17.6	$p<0.001$	Small
Symptom scales						
Fatigue	28.7	26.4	18.9	20.4	$p<0.001$	Small
Pain	13.0	22.4	14.2	20.9	p=0.54	Trivial
Nausea / vomiting	3.3	9.2	2.6	9.9	p=0.45	Trivial
Global Health Status	76.8	18.5	77.7	16.9	p=0.57	Trivial
FAS						
Total fatigue score	21.4	7.6	18.4	5.8	$p<0.001$	Yes
HADS						
Anxiety mean scores	4.7	4.2	3.8	4.3	$p<0.001$	No
Anxiety mean score in fatigue cases	7.6	4.5	6.5	4.0	p=0.31	No
Depression mean scores	3.7	3.8	3.4	3.2	p=0.02	No
Depression mean score in fatigue cases	6.6	4.1	6.4	4.0	p=0.83	No

Abbreviations: HL = Hodgkin lymphoma; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FAS = fatigue assessment scale; HADS = Hospital Anxiety and Depression Scale.

HL survivors and fatigued participants of the norm population (74.5 and 86.4 points respectively) than in the non-fatigued participants (HL survivors 95.7 and norm population 98 points). Differences are clinically relevant in both groups, and reflect a large difference in the HL survivors group and a medium difference in the norm population.

Clinical relevance of fatigue scores

Fatigue scores were significantly higher among HL survivors than in the norm population, and these differences were clinically relevant (Table 6.3). Mean QLQ-C30 fatigue scores differed 9.8 points (28.7 *vs* 18.9), reflecting a small but clinically relevant difference. The FAS total fatigue scores were 21.4 versus 18.4 points (>0.5 SD), which also reflects a clinically relevant (albeit small) difference.

Association of fatigue with patient and treatment factors and comorbid conditions

Multivariate regression analysis using the FAS scores showed that a lower level of education was associated with a higher risk of fatigue (Table 6.4). After adding clinical variables to the regression analysis, the significance of level of education disappeared, and having one to two comorbid conditions (OR 4.7) or > than 2 comorbid conditions (OR 17.5) were significantly associated with fatigue.

After adding psychological distress symptoms, however, the influence of comorbidities lacked statistical significance. Symptoms of depression (OR 1.8) and anxiety (OR 1.2) were the only factors significantly associated with high levels of fatigue.

Logistic regression analysis of the QLQ-C30 fatigue data did not differ from the FAS data (data not shown). Using the QLQ-C30 having one to two comorbidities (OR 3.0, 95% CI 1.3-7.3, p=0.02) and symptoms of depression (OR 1.2, 95% CI 1.1-1.4, p=0.04) were the only variables associated with fatigue.

Discussion

In this cross-sectional study, we found a higher prevalence rate of fatigue in HL survivors compared with an age- and sex-matched Dutch normative population of 15% and 18% using two different validated fatigue measures (QLQ-C30 fatigue and FAS respectively). We also observed a significant association between fatigue caseness and high levels of depression and anxiety, especially in the HL cohort. Mean fatigue levels were significantly increased in the HL survivors compared with the norm population, and differences were also found to be clinically relevant. Symptoms of depression and (to a lesser extent) anxiety and comorbidities were found to be the only variables associated with long-lasting fatigue.

One of the strengths of our study is that we measured fatigue through both a generic (QLQ-C30) and a fatigue-specific (FAS) questionnaire. Both questionnaires independently measured a significantly higher prevalence of fatigue in the HL survivors. We showed that the identification of fatigue cases between both questionnaires was consistent in 83% of the HL survivors and 81% of the norm population. Our data are robust, since missing items were < than 3%.

Our study not only showes that HL survivors more often suffer from chronic fatigue but also clearly shows an association between fatigue and depression or anxiety. We showed that a combination of both fatigue and anxiety occurred in 20% of

Table 6.4: Logistic model of factors associated with fatigue using the FAS TOTAL score

	Model: block 1			Model: block 1+2			Model: block 1+2+3		
Variables	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Block 1: Demographic variables									
Age	0.99	0.97-1.02	0.64	0.97	0.95-1.01	0.09	0.97	0.94-1.02	0.19
Male vs female	1.42	0.74-2.73	0.29	1.33	0.64-2.76	0.43	2.1	0.79-5.70	0.13
Education: low vs mid	**0.22**	**0.05-0.92**	**0.038**	0.27	0.05-1.37	0.11	0.78	0.06-8.93	0.84
Low vs high	**0.14**	**0.03-0.65**	**0.12**	0.29	0.05-1.65	0.16	1.38	0.10-18.72	0.80
Partner	0.51	0.24-1.08	0.08	0.54	0.24-1.25	0.15	0.41	0.13-1.24	0.12
Block 2: Clinical variables									
Time since diagnosis				0.97	0.86-1.11	0.73	0.96	0.81-1.15	0.70
No comorbidity vs 1-2				**4.73**	**2.10-10.64**	**<0.001**	2.76	0.93-8.12	0.06
No comorbidity vs >2				**17.49**	**4.27-71.51**	**<0.001**	4.25	0.68-26.39	0.12
Treatment: CT vs RT				0.69	0.77-6.09	0.73	1.22	0.09-16.03	0.88
Treatment: CT vs CMT				0.85	0.41-1.77	0.68	1.09	0.41-2.93	0.86
Block 3: Psychological variables									
HADS anxiety							**1.19**	**1.00-1.41**	**0.46**
HADS depression							**1.80**	**1.37-2.37**	**<0.001**

Abbreviations: FAS = Fatigue Assessment Scale; CT = chemotherapy; RT = radiotherapy; CMT = combined modality treatment; HADS = Hospital Anxiety and Depression Scale; OR = odds ratio; CI = confidence interval. **Bold entries are the values from regression analysis reflecting statistical significance.**

all HL survivors and of fatigue and depression in 17%, compared with 8% and 9%, respectively, in the norm population. This significant association between fatigue and anxiety and depression has also been described by Loge *et al.* (8). They reported high HADS scores (anxiety and depression combined) in 52% of 109 fatigued HL survivors. Their results, however, were not compared with a control group or to a norm population. Our study further showed that almost all (97%) HL survivors with symptoms of depression were also fatigued. As both studies were cross-sectional by design, it is difficult to evaluate whether fatigue and anxiety or depression are two separate entities both occurring more often in HL survivors, or whether fatigue is a consequence of these psychological conditions. The lower level of cognitive functioning that we observed among the HL survivors, reflected in symptoms such as loss of concentration, might be explained as a manifestation of the impact of fatigue and/or psychological distress. In our multivariate analysis, we showed that depression and, to a lesser extent, anxiety were significantly associated with fatigue. However, due to the design of our study, a causal relation between fatigue, anxiety and depression cannot be established.

In daily practice, fatigue in HL survivors has proven to be a prominent problem. Many survivors report to suffer from chronic fatigue, with often significant impact on daily activities, which has proven extremely difficult to treat. Studies evaluating interventions aimed at improvement of fatigue in cancer survivors have often shown improvement in physical endurance, but limited improvement in the subjective feeling of fatigue and lack of energy (33). Two recent meta-analyses concluded that exercise interventions in fatigued cancer patients had a near-moderate effect size in reducing fatigue at best (34, 35). Increased awareness of fatigue and of depression and anxiety among treating physicians is essential. However, fatigue is more common and need not be a symptom of depression or anxiety. Differentiating between these symptoms can be challenging in the clinical setting. A possible aid in defining depression could be to shift the focus from fatigue to other dimensions of depression. Symptoms of depression and anxiety could be amenable to treatment. Psychosocial therapies such as cognitive behavioral therapy or educational counseling have proven to be beneficial in reducing symptoms of anxiety and depression (34).

It might be beneficial for both patients suffering from fatigue and for patients with depression or anxiety to receive treatment by professionals, although through different methods of focused psychosocial support or specific coping strategies, which might result in a clinically meaningful reduction of fatigue. This approach, however, should be explored in future studies. Ideally, HL survivors suffering from chronic fatigue should be invited for a diagnostic interview to distinguish between fatigue and depression, and then randomly assigned to specific psychosocial therapies. As HL survivors are at risk for a variety of comorbid conditions due to late treatment

sequelae, such as cardiovascular diseases, which could predispose for higher levels of fatigue, we examined the possible association of fatigue and comorbid conditions (3, 36). Hodgkin lymphoma survivors self-reported depression more frequently than the norm population. Our multivariate analysis showed a trend for the association between self-reported comorbidities and fatigue. However, mean time since diagnosis and treatment in this survey was still relatively short (mean 4.6 years, range 6 – 122 months), which means that the majority of the cohort is not yet at risk for late treatment sequelae. Moreover, with a mean age of 46 years, a large part of both the cohort and the norm population would not yet suffer from serious comorbidities.

Rates of fatigue in HL survivors in this study (43% by using QLQ-C30 and 41% by using FAS) are slightly higher than the rates reported by others (7, 16, 19). These three studies reported fatigue rates of 26-30% in HL survivors, but all used the same HL cohort. More recent data on cancer-related fatigue in patients with other types of cancer using the EORTC QLQ-C30 and Multidimensional Fatigue Inventory showed prevalence rates of 36% to 48%, which are comparable to our results (37-40).

In conclusion, our results show a clinically relevant higher prevalence rate of fatigue in HL survivors when compared with an age- and sex- matched population. We also found a significant association between fatigue and anxiety or depression. The only factors significantly associated with high levels of fatigue were symptoms of depression and anxiety. This might have implications for the diagnosis and treatment of fatigue in the clinical setting, as psychosocial therapies have proven to be effective in reducing anxiety and depression, and could therefore be beneficial in reducing levels of fatigue as well. This should be further examined in future trials.

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chapter 7

General discussion and future perspectives

In this thesis long-term sequelae that Hodgkin lymphoma (HL) survivors may encounter have been investigated. Although modern treatment strategies have made HL a highly curable disease, there is a life-long increased risk of morbidity and mortality due to treatment. The diversity of these potential long-term adverse events highlights the wide spectrum of possible treatment-related toxicities HL survivors face after initial diagnosis and treatment. Both treatment with chemotherapy and radiotherapy increase the risk of secondary cancers. Epidemiological studies have shown that radiotherapy increases the relative risk of solid tumors, especially in patients treated at a young age, with a high total dose of radiotherapy or with large radiation fields (1). Risks progress from 10-15 years after initial treatment (2). The most common second malignancy is breast cancer in female HL survivors. Current follow-up guidelines recommend screening of patients at risk for developing radiation induced breast cancer.

Apart from second malignancies, HL survivors treated with mediastinal radiotherapy also have increased risk of late cardiac complications (3, 4). A wide spectrum of cardiovascular disease (CVD) can occur. In screening studies valvular disease, such as calcification or retraction, is observed in 40-60% of patients (5, 6). Also, conduction disorders due to fibrosis or direct damage to the conduction system have been frequently described. The relative risk of myocardial infarction in HL survivors is 3-fold increased, which might be due to radiation-induced coronary artery stenosis (7).

All these adverse effects can severely impact health-related quality of life (HRQL). The presence of long-term psychosocial issues, fatigue or lack of energy may cause additional deterioration of HRQL. The mechanism of persisting fatigue in HL survivors is complex and believed to be multifactorial (8). Patient- or treatment characteristics associated with fatigue or not well defined, and treating psychosocial symptoms such as fatigue, lack of energy or vitality have proven to be a clinical challenge.

Secondary tumors

An increased risk of treatment-related secondary tumors in HL survivors has been established in numerous epidemiological studies. A detailed overview of the risk of developing a second tumor was presented in **chapter 1**. The standardized incidence ratio (SIR) of secondary tumors in HL survivors compared to the general population ranges from 2-10 for different types of tumors. The risk of secondary skin cancers in HL survivors has not been extensively studied. In **chapter 2** we assessed the risk of secondary skin cancers in a large cohort of HL survivors treated at Leiden University Medical Center (LUMC). Skin cancers, and basal cell carcinoma (BCC) in particular, are the most common types of cancer in the general population in the Netherlands. To be able to compare risks established in our cohort with the general population we used data from the Comprehensive Cancer Centre South registration, as BCC are not registered in the Dutch Cancer Registry. We found an increased SIR of 5.2 for BCC in HL survivors compared to the general population. Our results complement the limited knowledge that existed concerning secondary-induced skin cancers in HL survivors.

The SIR is a measure of expressing the relative risk of developing a second cancer, compared to the general population. However, relative risks do not provide information on absolute numbers of additional cases of cancer and thus clinical relevance and burden of disease. This is better reflected in the absolute excess risk (AER), which is a way of defining the difference in absolute risks of second cancers compared to the general population. The AER expresses the number of additional second tumors on top of the number expected in the general population. BCC is a type of tumor frequently seen in the general Dutch population and incidence increases with older age. The absolute number of BCC in the general population is therefore high and an increased relative risk will result in a significant number of additional skin cancers; this is reflected in a strongly increased AER: the number of excess cases of BCC in HL survivors who are more than 20 years after initial treatment is more than 100 per 10.000 patients per year. Comparison of our results to existing literature is difficult, since data on secondary skin cancers in HL patients is limited. Swerdlow *et al.* (9) have reported risks of non-melanoma skin cancers (NMSC) in a large cohort of 1000 HL survivors treated between 1963 and 1989, of whom 80% were <45 years old at time of diagnosis. They report an overall SIR of 3.9 , which is lower than the rate that was found in our cohort but might be explained by the shorter mean follow-up time. Watt *et al.* (10) conducted a case-control study to evaluate the association between radiation dose on the skin and occurrence of NMSC. Cases were selected from a large cohort of childhood cancer survivors; 199 cases were identified of which 50% were HL survivors, treated before the age of 21 years. A significant dose-response relationship

was found; odd-ratios (OR) for developing NMSC increased from 3.5 at a skin dose of 1 to 5 Gy up to an OR of 22 at a skin dose of 25-35 Gy. These OR are much higher than the rates that were found in our study, but patient characteristics between the two cohorts were very different, as the childhood cohort only included patients who completed treatment before the age of 21 years. In our study we have shown that age at diagnosis is one of the most important factors in the risk of developing BCC.

BCC is a highly curable type of cancer. However, with larger tumors the risk of morbidity due to treatment interventions and even mortality increases. Increased awareness of the risk of secondary skin cancers both in patients but also in (treating) physicians is essential for early detection and treatment. This might be achieved by improving education on possible risks due to HL treatment in the setting of continuing training of physicians. Patients should be educated at the outpatient clinic and instructed to examine the skin for lesions, especially at the location of previous radiation treatment fields. Furthermore, the use of general preventative measures for the development of skin cancer such as reducing sun exposure and use of protective clothing and sun lotions are essential, and should be extensively discussed.

It is expected that risk of skin cancer for future HL patients will abate, due to the decreased skin exposure with the currently used smaller radiation treatment fields. On the other hand, for patients who have been treated with large radiotherapy fields in the past the total number of skin cancers is expected to further increase in the upcoming years due to increasing absolute risks with older age, thus implicating a substantial and clinically relevant issue.

Cardiovascular disease and screening

Over the past decade increasing evidence for an increased risk of CVD in HL survivors has been collected from epidemiological studies. Moreover, CVD accounts for major morbidity and is the most common nonmalignant cause of death at a relatively young age in HL survivors. Risks of myocardial infarction due to coronary artery disease (CAD) are 3-4 fold increased, with mediastinal radiation treatment as one of the most predominant risk factors for developing CAD (3, 4). Previous studies have shown that the course of CAD in HL survivors is often asymptomatic, even in the presence of severe coronary stenosis, which has fuelled the interest in the role of screening for CAD. Results from the first screening studies were disappointing, mainly because of low sensitivity and specificity rates of the screening instruments such as exercise stress testing (7). Golden standard for the diagnosis of CAD and its severity is invasive coronary angiography which is associated with a risk, albeit

small, of serious complications and even mortality and therefore deemed unsuitable for the purpose of screening. A more promising screening modality is the computed tomography coronary angiography (CTA). In symptomatic patients with an intermediate to high risk for CAD this non-invasive test has shown high diagnostic accuracy (11, 12). A limited number of screening studies with CTA in Hodgkin lymphoma survivors has been conducted. A small study consisting of 9 HL survivors showed high rates of CAD (13). Results however were confounded due to presence of cardiac risk factors in almost all patients. A larger study among 119 childhood HL survivors also reported a high rate of CAD on CTA (16%)(14). In this study only 50% of the participants were treated with mediastinal radiotherapy as part of their treatment and evaluation was done after a relative short follow-up period of 7 years. As the majority of abnormalities on CTA were non-significant stenosis, most patients did not receive further diagnostic interventions to confirm CTA results. Only 16% of participants with abnormal CTA scans underwent subsequent invasive coronary angiography, and a therapeutic intervention was performed in 1 patient.

Evidence for the role of CTA as a screening modality therefore remained limited and was further evaluated in our screening study among 48 HL survivors (**chapter 3**). In this phase II study participants underwent an extensive screening protocol, in which not only the role of screening by means of CTA was evaluated, but results were also related to screening by means of ECG exercise testing. Furthermore, patients with significant CAD on CTA subsequently underwent invasive coronary angiography to confirm CTA results and, if indicated, to undergo therapeutic interventions. In our study, we selected patients at a high risk of coronary abnormalities to evaluate the use of CTA as a screening modality, based on time since diagnosis and treatment with mediastinal radiotherapy. Of the 48 included patients, 45 had an evaluable CTA scan. Of these patients, 20% had significant CAD (>50% narrowing) on CTA, and another 22% had a non-significant stenosis with a lumen narrowing of 20-50%. This rate of abnormal CTA scans is higher than the rate found in childhood HL survivors by Küpeli *et al.* (14), which could be explained by differences in patient and initial treatment characteristics between the study populations, as in our study all patients had been treated with mediastinal radiotherapy and screening was performed after a significantly longer follow-up period. Significant coronary stenosis was verified by means of invasive coronary angiography in all but one patient with an abnormal CTA. In 7 (88%) out of our 8 patients who underwent coronary angiography (CAG) therapeutic interventions followed, in the majority of cases by means of revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). A small proportion was started on medical therapy. The intervention rate in our study was also higher than intervention rates in other screening studies, which again might be explained by differences in study population characteristics. Recently, Girinsky *et al.* reported the outcome of their CTA screening study among

179 asymptomatic HL survivors, all of whom who had been treated with mediastinal radiotherapy (15). In their analysis 26% were diagnosed with coronary artery lumen narrowing, of which 17% was intermediate or severe. Half of these patients underwent diagnostic angiography and a total of 6% eventually underwent a therapeutic surgical intervention. Again, these rates are lower than the 42% lumen narrowing and 11% of surgical interventions in our cohort, but the median interval between treatment and CTA in the study by Girinskyi was 9.5 years (range 0.5-40) compared to the longer interval of 21 years (range 11-29) in our study.

When relating CTA findings to the results of ECG stress testing, we found that these results did not correspond. In only one patient with an abnormal CTA scan the ECG stress test showed ischemia. None of the participants had typical symptoms of ischemia, such as anginal complaints, during stress testing. These findings confirm that ECG stress testing only visualizes distinct ischemia, while CTA is able to detect subclinical damage not (yet) resulting in detectable ischemia. A screening study among 294 HL survivors using ECG stress testing and radionuclide perfusion imaging showed that during a median follow-up period of 6.5 years after finishing screening 10% developed symptomatic coronary artery disease and 30% were diagnosed with a cardiac event, including 18% cardiac deaths (16). These results underline the fact that screening by means of ECG stress testing is not adequate in this population who do not present with typical and early signs of ischemia and thus should not be used as a screening modality.

Another possible screening modality would be the use of magnetic resonance imaging (MRI). No screening studies using MRI have been performed in HL survivors. However, several studies have been conducted to establish the role of MRI in detecting CAD in symptomatic patients, and therefore with a high disease prevalence (>70%). A meta-analysis of these studies has shown high sensitivity and specificity rates of CAD detection with MRI, although results vary considerably between studies (17). One of the advantages of screening by means of MRI is avoidance of ionizing radiation. However, the most promising aspect of MRI screening is the ability to visualize cardiac valves and myocardial wall movements in one single diagnostic test. Whether MRI is equally effective in a population with a low prevalence rate of CAD is as yet unknown. Both CTA and MRI screening require administration of medication to decrease the heart rate to optimise image quality and the use of intravenous contrast. In addition, MRI is an expensive diagnostic test, and relatively burdensome for patients due to the noise and long duration of image acquisition. At present, screening by means of CTA seems to be the most effective modality for screening, with respect to a high diagnostic accuracy even for detecting subclinical disease, cost-effectiveness and patient burden.

An essential prerequisite for justifying screening is that effective treatment for

screen-detected CAD is available. Ideally, detection and treatment of subclinical coronary artery stenosis should lead to a decrease in myocardial ischemia and infarction and thus to a decrease in the risk of cardiac morbidity and mortality. Since the development of subclinical disease into clinically apparent ischemia or myocardial infarction is uncertain and could possibly take years, this makes symptomatic cardiac disease a difficult endpoint to assess in a clinical study, especially in a relatively small population such as HL survivors. In our study no randomization between screening and no screening was performed, since we determined this to be unethical. Neither do we have long-term follow-up data of participants at present and therefore no information on occurrence of cardiac events after screening. Moreover, none of the other screening studies using CTA have reported on events after screening. Based on our current results we can therefore not assess the clinical benefits of screening and interventions in our asymptomatic population. However, a parallel can be drawn with results from cardiologic studies. In asymptomatic cardiac populations an overall survival benefit has been shown in patients with severe proximal left CAD who underwent subsequent interventions (18, 19). In our study population the majority of coronary stenoses were located in the ostium or proximal in the main coronary arteries, resulting in a large proportion of the heart at risk in the event of an occlusion. Among the patients with significant CAD on CTA who underwent subsequent invasive coronary angiography, two patients were diagnosed with severe main stem stenosis of >90%. Complete occlusion of the main stem would result in absence of blood flow to the entire heart. Our two patients with this severe occlusion reported no cardiac symptoms, not even during adequate stress testing. The high prevalence of proximal stenoses combined with the absence of accompanying warning symptoms, and overall survival benefits of treating such lesions shown in cardiac populations support the idea of screening in HL survivors.

However, screening has several potential disadvantages. Although the additional radiation exposure due to CTA is considered low (3-5 mSv) the tissue that is exposed is mainly breast tissue which often is already at risk of developing secondary breast cancer, especially in females. Also, diagnostic coronary angiography, performed to confirm CTA results, can cause serious complications. Based on our first results and the results from Girinsky *et al.* we can conclude that a population of asymptomatic HL survivors, more than 10 years after treatment with mediastinal radiotherapy, indeed has a substantial risk of about 20% of significant CAD on CTA, and approximately 5-10% will need therapeutic surgical interventions. However, this means that in the setting of screening 80% will not show any important abnormalities, but are exposed to the potential risks and burden of screening. Ideally, we would need to identify a high-risk subgroup within our HL survivor cohort, who are most at risk of developing CAD. However, the included number of patients was too small to be able

to identify a subgroup with the highest risk of abnormalities, such as those with other risk factors, longer time since treatment or treatment parameters such as specific location and dose of radiation fields. Girinsky *et al.* performed a multivariate analysis and showed that age <25 years at diagnosis, other cardiovascular risk factors such as hypertension or hypercholesterolemia but especially the dose at the origin of the coronary arteries were prognostic predictors for the prevalence of coronary artery stenosis (15).

Apart from selection for screening based on patient and treatment characteristics, recent interest has focused on the role of selection based on cardiac biomarkers. A wide range of markers has become available in recent years and are routinely used in the diagnostic setting in patients presenting with symptomatic CAD. One of the best known biomarkers is a hormone synthesized in the myocardium involved in the sodium and water balance; B-type natriuretic peptide (BNP). Release of BNP occurs in response to myocardial stretch, so it is said to be a measure of overall cardiac function. It is most easily measured in the form of N-terminal pro-BNP (NTpro-BNP), since this is a very stable molecule (20). Several studies have investigated the predictive role of NTpro-BNP in absence of symptomatic cardiac disease (20). Results however are conflicting. Some studies show a predictive value of NTpro-BNP for the risk of heart failure or major cardiovascular disease, others have failed to show a predictive value for coronary artery disease-related death. Based on these results, patient selection for screening solely on biomarkers cannot be recommended at present. Whether biomarkers will have additional value on top of selection for screening by CTA based on patient and treatment characteristics should be explored in clinical studies.

Other important aspects in the decision on whether or not to screen are cost-effectiveness, compliance and the evaluation of the perceived burden and benefits of screening. None of these aspects were evaluated in previous screening studies. In our pilot study, we did evaluate the perceived burden and benefits of screening and the influence of an extensive screening programme on health-related quality of life. We also assessed the influence of extensive counseling on CVD and screening on perceived information provision (**chapter 4**). Counseling and screening emphasize the possibility of serious, potentially life-threatening long-term complications of past treatments. We have shown that a confrontation with these risks, the anxiety this may cause and the psychological impact this may have, do not reduce the motivation of patients to participate in a screening programme. In general, the counseling on late treatment sequelae and screening tests were perceived as highly informative. This resulted in a significantly and clinically relevant improvement in satisfaction with information provision. The vast majority of patients were content with participating in the study. Although patients with screen detected abnormalities reported

the emphasis placed on late effects to be more burdensome than patients without abnormalities, there was no difference in satisfaction in participating in screening.

All in all, the question whether or not to screen has not been completely answered yet. We showed that for most patients, the perceived benefits of screening outweigh the burden of screening, and that patient satisfaction strongly increases with increased information provision on risk of late cardiac complications. However, the greatest challenge lies in an optimal patient selection for screening. Although CTA seems to be a sensitive and acceptable screening tool, current patient selection based on mediastinal radiotherapy and time since treatment results in prevalence of CAD on CTA of 20% and surgical interventions in 11%, thus exposing 80% of the selected patients to potential risks of screening, and 9% to potential risks of diagnostic angiography. Before deciding for screening in a standard fashion, further refinement of patient selection with factors such as radiation dose to the coronary arteries or additional cardiac risk factors such as hypertension, should be done preferably based on results from a larger scale cohort study, as is it unlikely that a randomised trials is feasible in this population. At present this is being implemented at the LUMC as part of the dedicated late effects outpatient clinic, and will probably be extended to other hospitals participating in the nationwide network of long-term HL follow-up clinics in the near future.

For all patients who are at risk of developing CAD, one of the most important preventive measures lies in patient education and control of cardiac risk factors. Many patients, especially those who are not in follow-up at a dedicated late effects clinic, are not aware of the magnitude of the risk of cardiovascular events due to their past treatment. Patient awareness and lifestyle measures such as a healthy diet, adequate physical activity and refraining from smoking are extremely important. With the additional irreversible risk factor for CVD in the form of past mediastinal radiation therapy it is of utmost importance to avoid all other cardiac risk factors as much as possible.

Health-related quality of life and fatigue

Historically, interest for late effects of treatment in the follow-up of HL survivors has been focused on the physical complications of treatment. However, in the past two decades increasing interest and understanding of the psychosomatic and psychosocial aspects of treatment and the burden of having survived cancer have developed. As HL is a disease that predominantly affects young adults the diagnosis, treatment

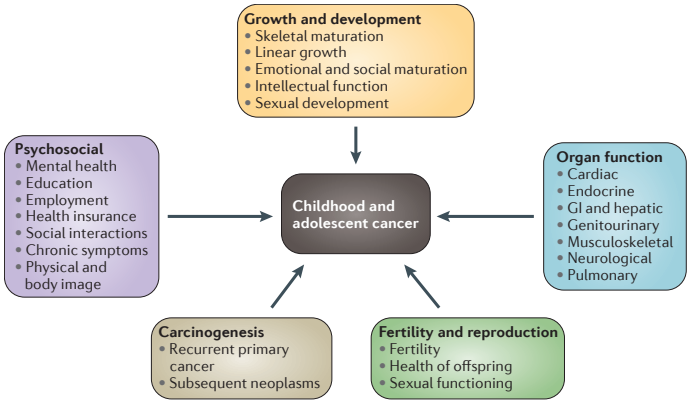

Figure 7.1: Range of health-related and quality of life outcomes among long-term survivors of childhood and adolescent cancers (21).

and late effects of treatment potentially affect a wide spectrum of psychosocial issues (Figure 7.1).

Facing the diagnosis of cancer confronts these young adults with their mortality, in an age period where most young adults never have to face such insecure issues and anxiety. Undergoing treatment severely impacts their normal life, and may require absence from school, work or family responsibilities. After treatment, distress concerning ongoing toxicities but also of late effects can severely influence health-related quality of life (HRQL). Chronic symptoms and emotional distress can result in difficulties to participate in productive work environment and affect the possibility to maintain normal social relationships. Studies have shown that 20-40% of cancer survivors come to face such difficulties (22). Young adulthood is a time period in which personal autonomy and development of an individual identity is established. This makes young adults especially vulnerable to insecurity, anxiety and emotional distress (21). The possible limitations in daily life, especially in comparison with healthy peers can be difficult to cope with. Of all psychosocial problems affecting cancer survivors one the most frequently reported symptoms is fatigue (23). Especially in young adult survivors of cancer, such as HL survivors, fatigue severely impacts HRQL. In fact, of all symptoms that affect cancer patients fatigue and lack of energy or vitality is reported to be most distressing (24). Fatigue can be present at diagnosis, worsen during treatment and often remains present after cure. The pathogenesis of cancer-related fatigue is not well understood, and is assumed to be a multifactorial process. Several studies have shown a dysregulation of inflammatory cytokines to be

associated with the presence of fatigue (25, 26). Increasing evidence demonstrates a role for a genetic predisposition (27). Other potential contributing factors are presence of physical symptoms such as pain or loss of appetite, tumor related factors such as anaemia or electrolyte disturbances (8).

The prevalence of persisting fatigue and predictors of fatigue in HL survivors have been evaluated in several studies. A review of the results of these studies is presented in this thesis (**chapter 5**). The prevalence of fatigue in HL survivors ranges between studies from 11% to 75%, and is significantly increased when compared to prevalence rates in age-matched healthy populations. Identification of clinical or treatment related factors predisposing for persisting fatigue remains challenging. Studies often encompass heterogeneous survivor cohorts, and longitudinal data are mostly lacking. Furthermore, results often contradict, which makes it difficult to draw firm conclusions. Our review showed that the only factor that systematically predicts persisting fatigue throughout these studies is increasing age at diagnosis, and no impact of stage of initial disease or treatment modality was shown. Only a few studies have evaluated the association between fatigue and physical (treatment-induced) comorbidities or psychiatric comorbid conditions. All of these studies showed increased prevalence of fatigue in patients with comorbid conditions or psychiatric disorders, which can be explained by the fact that these are also independent risk factors predicting fatigue. The association between psychosocial distress and fatigue was addressed in only one cross-sectional study, which showed that chronic fatigue and psychological distress are two separate phenomena occurring in HL survivors, though they are correlated. Unfortunately, results were not compared to a healthy norm population.

In **chapter 6** the association between comorbidities and anxiety or depression with fatigue was evaluated in patients recently treated for HL, and compared to data from an age- and sex matched Dutch norm population. Our results confirmed the increased prevalence of fatigue in HL survivors compared to the general population. The rate of more than 40% HL survivors reporting fatigue is comparable to recent fatigue data from survivors of other types of cancer. Our results confirm the association between fatigue and comorbidities. We also found a significant association between the presence of anxiety and depression and prevalence of fatigue. To fully comprehend the relation between these psychosomatic distress factors and fatigue is challenging. First of all, the clinical distinction between fatigue as a single issue and fatigue as part of a depression or anxiety disorder is often difficult to make, because in most anxiety or depression scales the presence of fatigue is one of the key aspects defining diagnosis. In the past decade there has been increasing awareness and interest among physicians for psychosocial issues. For patients, the recognition and acknowledgement of fatigue as a long-term complication of treatment has been an important first step. The next step however, treating fatigue, has proven to be one

of the most challenging problems in cancer care. Apart from cross-sectional studies assessing the prevalence of fatigue in HL survivors, there have been very few studies assessing the efficacy of different treatment strategies for fatigue. However, a parallel might be drawn with other types of cancer. In breast cancer patients there have been several studies evaluating the improvement of fatigue with physical exercise treatment. These studies often show improvement in physical endurance, but little improvement in the subjective feeling of tiredness or lack of energy. For adult cancer survivors psychosocial interventions such as cognitive behavioural therapies have also been evaluated in randomized controlled trials. In a meta-analysis of these trials a promising result was shown when interventions specifically focused on fatigue, such as educational sessions and coping strategies (28). The effect of such treatment however was moderate, and long-term follow up data to confirm prolonged effect of these interventions are needed. Especially in the setting of psychosocial interventions differentiating between fatigue and psychological distress and other issues may prove to be essential for optimizing further treatment strategies.

Conclusions

Awareness and recognition of long-term treatment related complications and problems have increased tremendously over the past decades, which has been an important first step. Many issues however have not been resolved. Screening for secondary malignancies, especially breast cancer has become standard of care. Awareness of secondary skin cancers should be increased, as shown by our analysis. Evidence for screening for cardiovascular disease, being the most common nonmalignant cause of death in HL survivors, is increasing. Screening by means of CTA is feasible and favourably evaluated, although further research is needed to optimize the selection of patients who will benefit most. The psychosocial aspects of treatment influencing quality of life have also gained increasing interest. Fatigue, as one of the most prominent symptoms, is significantly increased in HL survivors, although predisposing factors for persisting fatigue have been ill defined. Treating fatigue has proven to be a clinical challenge, although a first approach should be in differentiating fatigue from other psychosomatic distress factors. A personalized approach in which behavioural therapies and educational sessions play a key role should be further explored.

In view of the emerging evidence of late treatment-induced toxicities in 20-30% of HL survivors, the role of radiotherapy has been debated (16, 29). Several randomized trials have evaluated the possibility to omit radiotherapy in the treatment of early

stage HL, in order to reduce late complications in future HL survivors. A recent meta-analysis concluded that combined modality treatment is superior to treatment with chemotherapy alone in terms of local control and short-term overall survival (30). Whether or not this gain in overall survival will persist over time remains to be seen, due to the delayed morbidity and mortality of treatment related long-term toxicity. It is likely that combined treatment of chemo- and radiotherapy is not necessary for cure in all early stage HL survivors, and omission of radiotherapy may be possible in a majority of this group. However, optimal selection of patients benefitting most from combined treatment is essential. A first effort in selecting patients based on interim PET-CT results was done in the subgroup of early stage HL with favourable prognosis in the randomized EORTC H10 study. Recently, preliminary results of the interim analysis of this patient tailored approach have been published (31). These results were disappointing, showing an increase in local relapse in patients treated with chemotherapy alone. Further research to establish which patient should and should not be treated with combined modality treatment is needed.

For now, a large cohort of HL survivors exists who are at risk of late treatment sequelae due to treatment received in the past. A large proportion of these patients has been dismissed from follow-up clinics in the past, and might be unaware of potential risks. Moreover, as HL is a relatively rare form of cancer, many general practitioners and medical specialists who do not monitor HL survivors on a regular base will also be unaware of potential risks. Education of these patients and physicians is very important. The dedicated late effects outpatient clinics and its associated patient information website are an effective method for educating survivors. In consultation with patients an individual risk profile based on characteristics of previous treatment can be made, and from there a patient tailored survivorship care plan can be designed and discussed with each individual HL survivor. Implementation of this care plan can either be executed in the late treatment clinic, or in accordance with the treating general practitioner. At Leiden University Medical Center (LUMC) we have established the Hodgkin lymphoma late effects outpatient clinic in 2010; the "BETTER" clinic. It was the first dedicated clinic in the Netherlands focusing on physical and psychosocial aspects and complications of the treatment of HL and it was set up as part of the nationwide network of dedicated specialists engaged in this subject. In the near future, more of such clinics will be set up to ensure nationwide coverage. The dedicated HL outpatient clinics thus provide the possibility to accurately monitor future late effects. An essential aspect of these late treatment effect outpatient clinics is that they provide a unique platform for future research, in order to continuously optimise patient treatment and education.

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Summary

Chapter 1

Hodgkin lymphoma (HL) is a relatively rare haematological malignancy, predominantly affecting young adults. The outlook for cure for patients with HL is good, with 5-year overall survival rates of 80 to 90% for all stages combined, and around 95% for stages I-II. At present, treatment often consists of a combination of chemotherapy and radiotherapy with limited treatment fields, especially in those presenting with early stage disease. Over time it has become increasingly evident that the historically used extensive treatment fields for HL can potentially lead to numerous long-term adverse effects, often presenting clinically with a delay of more than 10-15 years after treatment. Secondary tumours - such as breast cancer induced by radiotherapy and non-Hodgkin lymphoma induced by chemotherapy - and cardiovascular diseases are the best known long-term adverse events after HL treatment. However, cross-sectional studies have also established long-term psychosocial and psychosomatic symptoms in HL survivors, although predisposing factors and evidence-based treatment options are still mostly lacking.

The objectives of this thesis were to address and investigate several late effects of radiation therapy in HL survivors that have not been extensively studied:

1. To evaluate the long-term risk of secondary skin cancers after radiotherapy in HL survivors, and compare these risks to the general Dutch population.
2. To investigate the feasibility of screening for coronary artery disease by means of computed tomography coronary angiography (CTA) in HL survivors, and evaluate satisfaction with information provision and the psychological burden of screening.

3. To assess the prevalence of fatigue in HL survivors compared with the general Dutch population, and evaluate associations with predisposing factors.

Chapter 2

Increased rates of secondary solid tumours are seen after exposure to radiation therapy. The evidence for the occurrence of secondary skin cancers in HL survivors is limited, and was evaluated in a retrospective cohort study among 889 HL survivors treated at Leiden University Medical Center. The incidence of secondary skin cancers following treatment for HL was investigated in comparison to an age-matched Dutch population, and the locations of the skin cancers were related to the radiation treatment fields. A total of 318 skin cancers were diagnosed in this HL cohort, the majority (93%) being basal cell carcinomas (BCC). The standardized incidence ratio (SIR, a measure of relative risk) of BCC in HL survivors was significantly increased compared with the general population (SIR 5.2, 95% confidence interval 4.0-6.6), especially in the group aged <35 years at diagnosis. Risks increased with longer follow-up; after 35 years the SIR was 15.9, resulting in 626 excess cases of BCC per 10.000 patients per year. The majority of skin cancers developed within the radiation treatment fields (57%). These results confirm that radiotherapy for HL is associated with a strongly increased long-term risk of developing skin cancers as compared with the general Dutch population. Patients treated at a young age have the highest risk, which is in accordance to incidence data from other types of radiation-induced solid tumours. Since the absolute risk of developing skin cancer increases with age, the total number of skin cancers is expected to rise even further with aging of our HL cohort, implicating a substantial and clinically relevant future health issue.

Chapter 3

An increased risk of cardiovascular diseases, and especially a 3-4 fold increased risk of myocardial infarction (MI) has been described in HL survivors, especially when mediastinal radiotherapy was part of the treatment. The role of screening for coronary artery disease (CAD), which could potentially lead to MI, is not well defined. One of the most promising modalities for screening in terms of diagnostic accuracy is the use of computed tomography coronary angiography (CTA), and feasibility of screening using CTA was studied in a phase II study among 48 HL survivors who

were at least 10 years after HL treatment. Participants underwent a comprehensive screening protocol including ECG stress testing and CTA. Eventually, 45 CTA scans were available for evaluation. Presence of CAD was evaluated and quantified. Patients with significant abnormalities underwent subsequent diagnostic testing and, if indicated, intervention. A prevalence of significant coronary stenosis on CTA of 20% (N=9) was found, which is significantly increased to the expected prevalence in the general population of 7% (p=0.01). A total of 7 patients underwent either invasive (N=5) or medical (N=2) interventions. Results from exercise testing showed poor correlation of ischemic changes to CTA findings. None of the participants suffered anginal complaints during stress testing, and only one patient with significant CAD on CTA had signs of ischemia during stress testing. Our results show a high prevalence of cardiac abnormalities, which were asymptomatic even in the presence of life-threatening CAD. Although CTA seems a promising and feasible modality for screening, before introducing CTA as standard screening of HL survivors, a larger cohort study should be performed to confirm our results and to further refine patient selection for screening.

Chapter 4

The results from our phase II study described in chapter 3 showed that cardiac screening by CTA is feasible. However, confrontation of HL survivors with possible cardiac disease may have a negative effect on psycho-social well-being. The perceived burden and distress of undergoing CTA screening, and the effect of cardiovascular counseling on perceived information provision are described in this chapter. In total, 43 out the 48 patients from the phase II study also participated in this quality of life evaluation and completed both baseline and end of study questionnaires. Undergoing CTA was perceived as bothersome by 24% of the participants, and 20% felt nervous about receiving the test results. Overall, 80% did not perceive the emphasis that was placed on possible late cardiac effects of HL treatment by this screening study as bothersome, and 93% were highly satisfied with participating in the study. There were no differences between patients with or without screen-detected abnormalities. Perceived information on disease, medical tests and treatment increased significantly after screening ($p<0.01$). Differences were clinically relevant. Screening by means of CTA was highly valued and the benefits were felt to outweigh the emotional and practical burden.

Chapter 5

Survivors of HL are at risk of adverse psychosocial or (psycho)somatic events as a result of cancer diagnosis and treatment. Fatigue, often described as severe loss of energy or loss of vitality is one the symptoms reported to interfere most frequently with daily life. A systematic review of studies on prevalence and severity of fatigue, and on predisposing factors for persisting fatigue was conducted. The majority of the 22 included studies were of cross-sectional design, thus including heterogeneous patient populations and limiting the possibility to evaluate causal relationships between fatigue and predisposing factors. Prevalence rates of fatigue were significantly higher among HL survivors compared with the general population. In studies comparing the severity of fatigue in HL survivors to an age- and sex matched norm population, all but the two smallest studies reported statistically significant higher levels of fatigue in HL survivors. Differences were mostly clinically relevant. None of the studies showed an association between stage of disease at initial diagnosis and fatigue. Both increasing age at diagnosis and the presence of comorbid conditions were associated with risk of persisting fatigue. Evidence for the influence of other patient- or treatment characteristics on persisting fatigue was often contradictory between studies, preventing any firm conclusions concerning these factors.

Chapter 6

To investigate the prevalence and severity of fatigue in Dutch HL survivors we conducted a study of health-related quality of life among 267 HL survivors. The response rate was 68% and the mean follow-up duration was 4.6 years. Results were compared to an age- and sex matched selection from a Dutch reference population cohort. Furthermore, the association between fatigue and presence of anxiety and depression was investigated. Fatigue was measured both through a fatigue-specific questionnaire (FAS) as well as part of a generic health-related quality of life questionnaire (EORTC QLQ C-30). Both questionnaires showed a statistically significant and clinically relevant higher prevalence rate of fatigue in the HL cohort. The multivariate analysis showed a strong and significant association between high levels of fatigue and depression (odds ratio 1.8, 95% confidence interval 1.4-2.4) and was also associated with anxiety and comorbidity (odds ratio 1.2, 95% confidence interval 1.0-1.4 and OR 3.0, 95% CI 1.3-7.3 respectively). Treatment of fatigue has proven to be a clinical challenge. The distinction between fatigue and symptoms of depression or anxiety may prove to be beneficial in the clinical setting, since depression and anxiety may

be amenable to psychosocial interventions such as cognitive behavioural therapies or medication.

Chapter 7

In this chapter the main findings of this thesis are presented, and their implications for adapting future follow-up strategies in order to improve after care for HL survivors are discussed and put into clinical perspective. HL survivors have an increased risk of developing secondary skin cancers, especially basal cell carcinomas. The standardized incidence ratio (SIR) for this type of skin cancer is 5.2, and even higher relative risks are found in patients who were treated at an age younger than 35 years. Along with increasing absolute risks with aging in general, the total number of skin cancers in HL survivors is expected to increase even further in the coming years. Although BCC is a curable type of cancer, early detection can prevent morbidity due to extensive surgical interventions and even mortality. Increased awareness among physicians and patients, and patient education with regard to preventative measures and regular skin inspection is of utmost importance.

HL survivors are at risk of developing cardiac disease due to their treatment. After mediastinal radiotherapy an increased risk of coronary artery disease (CAD) is found. As the course of CAD is often asymptomatic, the question of screening was raised. We have shown that the prevalence of screen-detected CAD by means of CTA is high, with 20% significant CAD and 22% non-significant lumen narrowing in 45 patients who had an evaluable CTA scan. The majority of patients with significant disease (88%) underwent subsequent intervention. Prevalence rates in our study are higher than other screening studies, which is explained by our selection of high risk patients, with a follow-up duration of more than 10 years. A health-related quality of life assessment was conducted as part of our study, which demonstrated that for the majority of patients the perceived benefits of screening outweighed the practical and emotional burden. Although screening seems well tolerated and prevalence rates of CAD on CTA are high, our current patient selection for screening would result in a 80% rate of patients exposed to potential risks, costs and burden of screening, but without significant abnormalities. This justifies further research, in order to identify a subgroup of HL survivors who would benefit most from screening. Further future refinement of patient selection might come from research identifying biomarkers, for the risk of cardiac disease. A crucial role in decreasing the number of cardiovascular events in HL survivors, lies in patient education and lifestyle measures, and control of cardiac risk factors such as smoking, hypertension or diabetes.

Apart from the range of long-term physical complications HL survivors can de-

velop over time, many of them also face long-term psychosocial and psychosomatic events. One of symptoms that can greatly impact health-related quality of life is persisting fatigue. In our systematic review we showed both prevalence and severity of fatigue to be significantly higher in HL survivors than in the general population. The identification of predisposing factors for fatigue is, unfortunately, often hampered by study design.

For patients, acknowledgement of fatigue as a genuine long-term complication has been an important first step. However, the challenge that remains is to find an effective treatment for persisting fatigue. We showed a strong association between fatigue and symptoms of anxiety and depression in HL survivors. The distinction between these symptoms may offer a first beneficial treatment step, since anxiety and depression might be amenable to psychosocial therapies.

Conclusions

In view of the emerging evidence of late treatment-induced toxicities in 20-30% of HL survivors, the role of radiotherapy has been debated. As for now, studies have shown superior local control and short-term overall survival when radiotherapy is part of HL treatment. With the delay of 10-15 years until clinical presentation of potential radiotherapy-induced morbidity and mortality is encountered it remains to be seen whether these short-term benefits will translate in a long-term overall survival benefit. It is likely that only a subgroup of patients benefits from the addition of radiotherapy, although more research is needed to identify this group. The risk of radiation induced late sequalae is expected to further decrease with the development of new radiotherapy techniques and decreasing the total radiotherapy dose en fields.

For now however, there is a large group of HL survivors who are at risk of late treatment sequelae, of whom a proportion remains unaware of potential risks. Identifying these patients and informing them of risks is important, and is currently being done in the setting of specialised late effects outpatient clinics. Also, the patient and health professional information website www.beternahodgkin.nl which has been developed by the late effects consortium 'BETER' is an easily accessible method for improving information provision. The dedicated outpatient clinics furthermore provide a unique possibility to monitor future late effects, and provide a research platform for screening and interventions and to further develop evidence based follow-up guidelines for this group of patients.

Nederlandse samenvatting

Hoofdstuk 1

Het Hodgkinlymfoom (HL, lymfklierkanker van het Hodgkin-type) is een relatief zeldzame hematologische maligniteit, die voornamelijk bij jongvolwassenen voorkomt. De kans op genezing van HL is groot: de 5-jaarsoverleving ligt voor vroege stadia (stadium I-II) rond de 95%, en voor alle stadia samen tussen de 80 en 90%. De behandeling van patiënten met HL bestaat tegenwoordig vaak uit een combinatie van chemotherapie en radiotherapie met gebruik van relatief kleine bestralingsvelden en gematigde dosis, vooral bij patiënten die zich presenteren met een vroeg ziektestadium. In de loop van de afgelopen jaren is het duidelijk geworden dat de in het verleden gegeven behandeling voor HL met zeer uitgebreide bestralingsvelden en hogere dosis een groot aantal langetermijnproblemen tot gevolg kan hebben, die zich vaak pas 10-15 jaar na behandeling presenteren. De meest bekende langetermijngevolgen zijn secundaire tumoren (zoals borstkanker geïnduceerd door behandeling met radiotherapie of non-Hodgkinlymfoom door behandeling met chemotherapie) en cardiovasculaire schade (zoals kransslagadervernauwing). Een aantal studies heeft inmiddels ook aangetoond dat HL-overlevenden kunnen kampen met psychosociale en psychosomatische langetermijnproblemen, zoals chronische vermoeidheid, angst en depressie, hoewel predisponerende factoren hiervoor niet duidelijk zijn en evidence-based behandelopties tot op heden grotendeels ontbreken.

De doelstellingen van de studies in dit proefschrift waren om een aantal late gevolgen van radiotherapie bij overlevenden van HL, die nog niet uitgebreid bestudeerd zijn, in kaart te brengen; specifieke doelen waren:

1. Na te gaan of het risico op geïnduceerde huidtumoren na radiotherapie bij HL overlevenden verhoogd is, en hoe hoog deze risico's zijn in vergelijking met de algemene Nederlandse bevolking.

2. Na te gaan of screenen op vernauwing van coronairvaten door middel van CT-coronair angiografie bij HL overlevenden zinvol is, en te evalueren hoe de tevredenheid met de informatievoorziening rondom screening en de psychologische belasting van screening zijn.
3. Na te gaan hoe vaak chronische vermoeidheid onder HL-overlevenden voorkomt in vergelijking met de algemene Nederlandse bevolking, en te onderzoeken wat de predisponerende factoren zijn.

Hoofdstuk 2

Radiotherapie geeft een verhoogd risico op geïnduceerde solide tumoren, die optreden vanaf 10-15 jaar na de radiotherapie. Er is tot op heden weinig bekend over het voorkomen van (mogelijk geïnduceerde) huidtumoren bij overlevenden van HL. In een retrospectieve cohortstudie onder 889 HL-overlevenden die behandeld waren in het Leids Universitair Medisch Centrum werd het voorkomen van huidtumoren onderzocht. De incidentie van huidtumoren werd vergeleken met een voor de leeftijd gematchte Nederlandse populatie, en werd voor iedere patiënt gerelateerd aan de eerdere bestralingsvelden. In dit cohort van 889 overlevenden van HL werden in totaal 318 huidtumoren gediagnosticeerd, waarvan het merendeel (93%) bestond uit basaalcelcarcinomen (BCC). De standaard incidentie ratio (SIR) van BCC in HL-overlevenden was significant (5x) verhoogd in vergelijking met de gematchte algemene bevolking (SIR 5.2, 95% betrouwbaarheidsinterval 4.0-6.6), vooral in de groep overlevenden die bij diagnose HL jonger dan 35 jaar waren. Risico's op BCC namen toe met duur van follow-up; na 35 jaar was de SIR 15.9, hetgeen resulteert in een extra aantal gediagnosticeerde tumoren van 626 BCC's per 10.000 patiënten per jaar. Het merendeel van de huidtumoren ontwikkelde zich binnen de bestralingsvelden (57%), en op aan zonlicht blootgestelde lichaamsdelen. De gevonden resultaten bevestigen dat radiotherapie, zoals gebruikt in de behandeling van HL, is geassocieerd met een sterk verhoogd langetermijnrisico op het ontwikkelen van huidtumoren in vergelijking met de algemene Nederlandse bevolking. Patiënten die op jonge leeftijd behandeld zijn lopen het grootste risico, hetgeen overeenkomt met het risico op andere radiotherapie-geïnduceerde solide tumoren zoals borstkanker. Gezien het feit dat het absolute risico op het ontwikkelen van huidkanker toeneemt bij ouder worden, is de verwachting dat het totaal aantal huidtumoren in het HL cohort nog sterk zal toenemen. Patiënten die in het verleden zijn behandeld voor HL en hun artsen moeten hierop alert zijn, zodat diagnostiek en behandeling in een vroeg stadium kunnen plaatsvinden.

Hoofdstuk 3

Bij langetermijnoverlevenden van HL wordt na bestraling van de lymfklieren in de borstholte (mediastinale radiotherapie) een verhoogd risico op cardiovasculaire aandoeningen beschreven, met name een 3-4 keer verhoogd risico op een krijgen van een myocardinfarct (MI) door kransslagadervernauwing. De rol van screenen op vernauwing van de kransslagaders (coronair sclerose), hetgeen meestal ten grondslag ligt aan een MI, is nog niet goed omschreven. Een van de meest veelbelovende modaliteiten om mee te screenen vanwege een hoge diagnostische accuraatheid, is het gebruik van de CT-scan van de kransslagaderen (CTA). De haalbaarheid van screening met behulp van CTA werd onderzocht in een fase-II-studie met 48 ex-patiënten die tenminste 10 jaar ziektevrij waren na hun behandeling voor HL. Deelnemers aan de studie ondergingen een uitgebreide cardiologische screening, onder andere bestaand uit een ECG-stresstest (fietsproef) en een CTA. Uiteindelijk waren er 45 CTA scans beschikbaar voor evaluatie. Aanwezigheid van kransslagadervernauwing werd gescoord en patiënten met ernstige afwijkingen, gedefinieerd als een vernauwing van tenminste 50% van de doorsnede van de kransslagader, werden verwezen voor aanvullend diagnostisch onderzoek en afhankelijk van de uitkomst daarvan voor interventie. De prevalentie van ernstige kransslagadervernauwing op CTA was 20% (N=9), hetgeen significant hoger was dan de verwachte prevalentie van 7% in de algemene bevolking van dezelfde leeftijd (p=0.01). In totaal ondergingen 7 patiënten een chirurgische interventie (N=5) of een medicamenteuze interventie (N=2). De correlatie tussen een afwijkende ECG-stresstest en een afwijkende CTA was laag. Geen van de deelnemers kreeg tijdens de ECG-stresstest klachten van pijn op de borst, en slechts één patiënt met significante coronair sclerose op CTA had tekenen van ischemie tijdens de stresstest. Onze resultaten tonen een hoge prevalentie van cardiale afwijkingen bij patiënten die in het verleden voor HL zijn behandeld en die zelfs in de aanwezigheid van levensbedreigende kransslagadervernauwing geen cardiale klachten aangaven. Ondanks het feit dat CTA een veelbelovende en goed uitvoerbare modaliteit voor screening lijkt te zijn, moeten, voordat een dergelijke screening definitief wordt ingevoerd, onze resultaten bevestigd worden in een grotere cohortstudie. Ook moet er gekeken worden of er een betere selectie van HL-patiënten voor wie CTA screening zinvol is kan worden gemaakt, door onderzoek te doen naar sterkere risicofactoren.

Hoofdstuk 4

De resultaten van de fase-II-studie beschreven in hoofdstuk 3 toonden dat cardiale screening door middel van CTA goed uitvoerbaar is. Echter, de confrontatie met mogelijke cardiale afwijkingen kan een negatieve impact hebben op het psychisch welzijn van patiënten. De psychische en fysieke belasting van het ondergaan van een CTA, en het effect van cardiovasculaire counseling op tevredenheid met informatievoorziening worden beschreven in hoofdstuk 4. In totaal deden 43 van de 48 deelnemers van de fase-II-studie mee aan deze kwaliteit van leven evaluatie. Zij vulden zowel voorafgaand als na afloop van het screeningstraject een aantal vragenlijsten in, die gericht waren op informatievoorziening, kwaliteit van leven en de psychische belasting van de confrontatie met de mogelijke cardiale risico's. Het ondergaan van een CTA werd door 24% van de deelnemers als belastend ervaren, en 20% was zenuwachtig voor krijgen van de uitslagen van de scan. De nadruk die door het screeningsonderzoek werd gelegd op mogelijke cardiale afwijkingen werd door 80% van de deelnemers als niet belastend ervaren, en 93% was ook achteraf tevreden over meedoen aan het onderzoek. Er waren hierin geen verschillen tussen ex-patiënten met en patiënten zonder afwijkingen bij screening. De informatievoorziening met betrekking tot ziekte, medische tests en behandeling en kennis daarvan waren significant verbeterd na afloop van het screeningstraject (p=0.01). Deze verschillen waren ook klinisch relevant. Screening door middel van CTA werd door de deelnemers positief gewaardeerd, en de voordelen van screening wogen bij de grote meerderheid op tegen de emotionele en praktische belasting.

Hoofdstuk 5

Mannen en vrouwen die in het verleden zijn behandeld voor HL lopen ten gevolge van de diagnose en behandeling ook het risico blijvende psychosociale of psychosomatische klachten te ontwikkelen. Vermoeidheid, ook wel beschreven als verlies van energie, het gevoel 'dat de batterij leeg is' of sterke lusteloosheid, is een van de symptomen waarvan ex-HL-patiënten aangeven dat die de kwaliteit van het dagelijks leven het meest beïnvloedt. Een systematische review werd verricht van studies met betrekking tot het voorkomen (prevalentie) en de mate van vermoeidheid, en van studies die predisponerende factoren voor vermoeidheid analyseerden. De meerderheid van de 22 geïncludeerde studies had een dwarsdoorsnede (cross-sectionele) opzet, hetgeen betekent dat de patiënten die geïncludeerd waren onderling vaak veel verschilden, waardoor een causaal verband tussen vermoeidheid en voorspellende factoren niet goed te leggen was.

De prevalentie van vermoeidheid onder HL-overlevenden was significant hoger dan in de algemene populatie. Studies waarin de ernst van vermoeidheidklachten onder HL-overlevenden vergeleken werd met qua leeftijd en geslacht gelijke groep uit de algemene bevolking toonden, behoudens in de twee kleinste studies, een statistisch significante zwaardere (ernstigere) vermoeidheid in de groep van HL-overlevenden. De gevonden verschillen waren in de meeste studies ook klinisch relevant. Geen van de studies toonde een associatie tussen het stadium van de ziekte bij diagnose en vermoeidheid. Zowel een hogere leeftijd bij diagnose als de aanwezigheid van andere aandoeningen (comorbiditeit) waren geassocieerd met een risico op chronische vermoeidheidsklachten. Resultaten met betrekking tot de invloed van andere patiënt- of behandelkarakteristieken op blijvende en ernstige vermoeidheidsklachten waren vaak tegenstrijdig, waardoor een harde conclusie omtrent deze factoren niet mogelijk was.

Hoofdstuk 6

Het voorkomen en de ernst van blijvende vermoeidheid onder Nederlandse ex-HL-patiënten werd onderzocht in een kwaliteit-van-leven-studie onder 267 HL-overlevenden. Het responspercentage was 68% en de gemiddelde follow-up-duur na de diagnose HL was 4.6 jaar. De resultaten werden vergeleken met een voor leeftijd en geslacht gematchte selectie uit een Nederlands referentiecohort, representatief voor de algemene bevolking. Ook werd gekeken naar de associatie tussen vermoeidheid en symptomen van angst of depressie. Vermoeidheid werd gemeten door middel van twee vragenlijsten, zowel een specifieke vragenlijst voor vermoeidheid (FAS) als met een subschaal over vermoeidheid uit de algemene Europese kwaliteit-van-leven-vragenlijst voor kanker (EORTC QLQ-C30). Beide vragenlijsten toonden een statistisch significante en klinisch relevante hogere prevalentie van vermoeidheid in het cohort van HL-overlevenden. De verrichte multivariate analyse toonde een sterk en significant verband tussen een hoger niveau van vermoeidheidsklachten en symptomen van depressie (odds ratio 1.8, 95% betrouwbaarheidsinterval 1.4-2.4) en een ook met symptomen van angst en met comorbiditeit (respectievelijk odds ratio 1.2, 95% betrouwbaarheidsinterval 1.0-1.4 en odds ratio 3.0, 95% betrouwbaarheidsinterval 1.3-7.3). In de klinische praktijk is chronische vermoeidheid een moeilijk te behandelen symptoom gebleken. Mogelijk is het onderscheid tussen vermoeidheid en symptomen van angst of depressie hierbij belangrijk, omdat angst en depressie te behandelen zijn met psychosociale interventies zoals cognitieve gedragstherapie of met medicijnen.

Hoofdstuk 7

In dit hoofdstuk wordt een overzicht gegeven van de belangrijkste bevindingen van dit proefschrift, en worden de implicaties hiervan voor verder onderzoek, begeleiding en voor follow-up-richtlijnen in perspectief geplaatst, om zo de nazorg voor overlevenden van HL verder te verbeteren. HL-overlevenden hebben een verhoogd risico op het ontwikkelen van een secundaire huidtumor, vooral basaalcelcarcinomen (BCC). Het risico op het krijgen van een BCC is 5x zo groot als voor een leeftijdgenoot in de algemene bevolking, en dit relatieve risico ligt nog hoger voor patiënten die behandeld zijn op een leeftijd onder de 35 jaar. Gezien het toenemend absoluut risico op BCC met hogere leeftijd zal het totaal aantal huidtumoren dat voorkomt bij HL-overlevenden naar verwachting nog verder stijgen. BCC is een goed te genezen vorm van huidkanker, maar vroegtijdige ontdekking ervan kan ervoor zorgen dat de behandeling minder ingrijpend hoeft te zijn, en kan zelfs de kans op uiteindelijke sterfte beperken. Bewustwording van deze risico's bij artsen en patiënten, voorlichting met betrekking tot preventieve maatregelen (vermindering van blootstelling aan de zon, beschermende kleding e.d.) en regelmatige inspectie van de huid zijn daarom erg belangrijk.

Overlevenden van HL hebben door hun behandeling ook een verhoogd risico op het ontwikkelen van hart- en vaatziekten (HVZ). Omdat dit vaak geen of weinig symptomen geeft, is de rol van screening op kransslagadervernauwing (coronair sclerose) onderzocht. Onze studie, waarin de kransslagaderen werden afgebeeld door middel van een CT-scan van de kransslagaderen (CTA) toonde bij 20% van de patiënten een ernstige vernauwing (meer dan 50% vernauwing) van de kransslagaderen. Daarnaast werd bij 22% een niet-significante vernauwing (een vernauwing van het vat van tussen de 30-50%) gezien. Het merendeel van patiënten met ernstige afwijkingen (88%) onderging daarna een behandeling. Ernstige afwijkingen werden in onze studiegroep vaker gevonden dan in andere screeningsstudies, waarschijnlijk omdat patiënten in onze studie een relatief hoog risico hadden, omdat zij tenminste 10 jaar na behandeling moesten zijn om mee te mogen doen. Om na te gaan of het proces van screenen en de nadruk die door screenen gelegd wordt op de kans op levensbedreigende complicaties van de vroegere HL-behandeling als belastend wordt ervaren, werd er een kwaliteit-van-leven-evaluatie gedaan als onderdeel van de screeningsstudie. Deze toonde aan dat voor het merendeel van de ex-patiënten de voordelen van de kennis rond de risico's en het screeningsonderzoek, waardoor meer zekerheid werd gekregen opwogen tegen de praktische uitvoering en belasting van het ondergaan van screening. Alhoewel screening weinig nadelige effecten had, en het voorkomen van coronair sclerose hoog was, leidt de huidige selectie voor screening ertoe dat er

in 80% van de gevallen geen belangrijke afwijkingen worden gevonden, terwijl deze ex-patiënten wel de risico's en belasting van screenen ondergaan. Verder onderzoek lijkt dus geïndiceerd, om een subgroep van patiënten te kunnen identificeren die de meeste baat van screening zal hebben. In de toekomst zal verdere verfijning van patiëntselectie mogelijk kunnen plaatsvinden op basis van bepaling van biomarkers, hoewel er meer klinisch onderzoek nodig is om de prognostische waarde hiervan voor het optreden van HVZ te bevestigen. Een cruciale rol in het voorkomen van HVZ bij HL-overlevenden ligt in voorlichting met betrekking tot risico's, aanpassingen in leefstijl en controle op andere cardiale risicofactoren zoals roken, hypertensie of diabetes.

Naast de lange-termijn fysieke complicaties die na behandeling van HL kunnen optreden, kunnen patiënten ook lijden aan psychosociale en psychosomatische problemen. Een van de symptomen die een grote negatieve invloed heeft op de ervaren kwaliteit van leven is chronische vermoeidheid. In onze systematische review hebben we laten zien dat zowel het voorkomen van vermoeidheid als de ernst van vermoeidheidsklachten significant hoger is in de groep HL-overlevenden dan in de algemene populatie. De identificatie van prognostische factoren wordt bemoeilijkt door onderzoeksopzet van veel studies. Voor veel patiënten is de erkenning van vermoeidheid als een langetermijneffect van behandeling een belangrijke eerste stap geweest. Echter, behandeling van vermoeidheidsklachten is in praktijk moeilijk gebleken. We hebben aangetoond dat er een sterk verband bestaat tussen vermoeidheid en symptomen van angst en depressie. Het onderscheid tussen deze symptomen is mogelijk een eerste belangrijke stap, gezien het feit dat angst en depressie mogelijk te behandelen zijn met psychosociale therapieën.

Conclusies

Ongeveer 20-30% van de ex-HL-patiënten ontwikkelt late behandelingsgerelateerde toxiciteit. Over de rol van radiotherapie in de behandeling van HL wordt veel gediscussieerd. Tot op heden heeft onderzoek naar weglaten van radiotherapie als onderdeel van de behandeling aangetoond dat met plaatselijke radiotherapie op de oorspronkelijk aangedane gebieden bij vroeg stadium HL de lokale controle en kortetermijnoverleving superieur zijn ten opzichte van behandeling met alleen chemotherapie. Omdat er tussen behandeling en het optreden van radiotherapie-geassocieerde langetermijneffecten een interval van 10-15 jaar zit, is het onzeker of dit zich ook vertaalt in een langetermijnoverlevingswinst. De verwachting is dat door verfijning van de radiotherapietechnieken, het gebruik van een lagere radiotherapiedosis en veel

minder uitgebreide radiotherapievelden voor de behandeling van Hodgkinlymfoom het risico op het optreden van late effecten sterk zal afnemen.

Voor nu bestaat er echter een grote groep HL-overlevenden die risico lopen op langetermijngevolgen van behandeling, waarvan een gedeelte niet op de hoogte is van deze risico's. Het identificeren van deze patiëntgroep en goede, op maat gemaakte voorlichting is belangrijk, en wordt momenteel gedaan als onderdeel van het landelijke consortium van late-effecten-poliklinieken. De website www.beternahodgkin.nl, die is ontwikkeld door het 'BETER' consortium is een toegankelijke manier om voorlichting aan patiënten en hulpverleners te verbeteren. De late-effecten-poliklinieken bieden daarnaast een unieke mogelijkheid om late effecten te monitoren, en bieden de mogelijkheid om onderzoek te doen en evidence-based follow-up richtlijnen verder te ontwikkelen voor deze groep patiënten.

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Curriculum Vitae

Laurien Daniëls werd geboren op 7 december 1980 te Haarlem. Zij behaalde in 1999 haar VWO diploma aan het Stedelijk Gymnasium te Haarlem. Na een jaar reizen en vrijwilligerswerk, startte zij in 2000 met haar studie Geneeskunde aan de Universiteit van Amsterdam. Haar wetenschapsstage deed zij op de afdeling Medische Oncologie in het Academisch Medisch Centrum in Amsterdam en het Nederlands Kanker Instituut – Antoni van Leeuwenhoek ziekenhuis, waarna zij in 2005 haar doctoraal examen behaalde. In 2007 liep zij een klinische stage op de spoedeisende hulp in het Kings College Hospital in Londen, en rondde hierna haar artsexamen af.

Na het artsexamen was zij achtereenvolgens werkzaam op de afdeling Interne Geneeskunde van het Amstelland Ziekenhuis in Amstelveen (hoofd: dr. C. Rustemeijer), en de afdeling Intensive Care in het Slotervaart Ziekenhuis te Amsterdam (hoofd: dr. G.H. Kluge). In 2009 koos zij definitief voor de Oncologie en startte met de opleiding tot radiotherapeut-oncoloog in het Leids Universitair Medisch Centrum (opleider: Prof dr C.A.M. Marijnen), hetgeen zij combineerde met een promotietraject naar late effecten van behandeling van Hodgkin lymfoom. De opleiding combineerde zij tevens met het lidmaatschap en uiteindelijk vicevoorzitterschap van de Landelijke Vereniging voor Arts-Assistenten (LVAG). In oktober 2014 zal zij haar opleiding tot radiotherapeut-oncoloog afronden.

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