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-

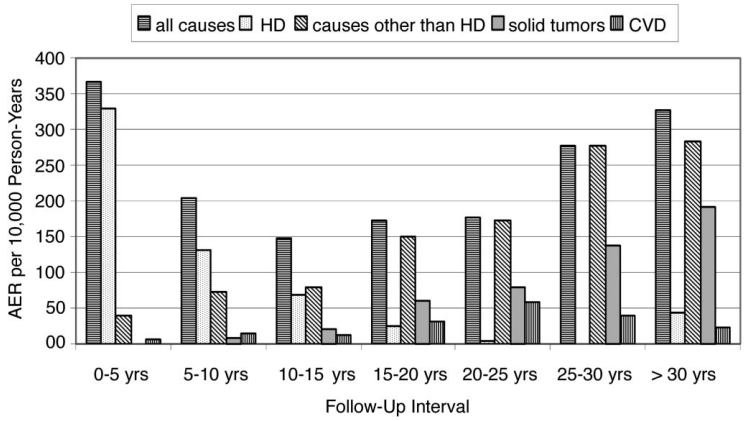

Figure 1.1: Absolute excess mortality from various disease categories over time, from a cohort of 1261 HL survivors. Mortality from HD decrease, while mortality due to solitary tumors and cardiovascular disease increase over time (23). HD = Hodgkin disease, CVD = cardiovascular disease AER = absolute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

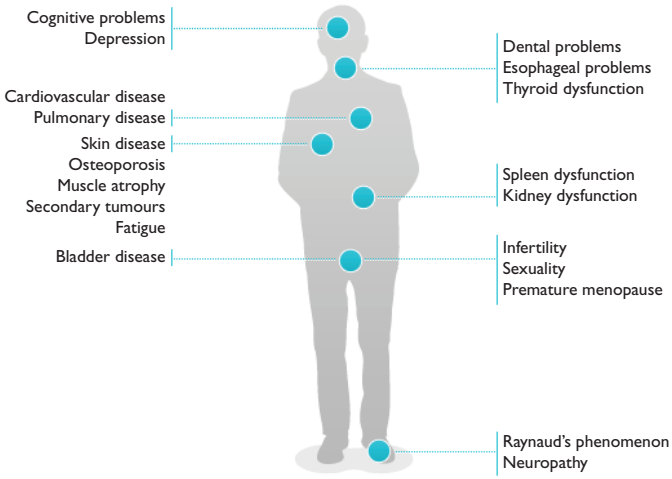

Figure 1.2: An overview of possible late treatment sequelae after treatment with chemotherapy, radiotherapy or a combination of these modalities (24).

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.

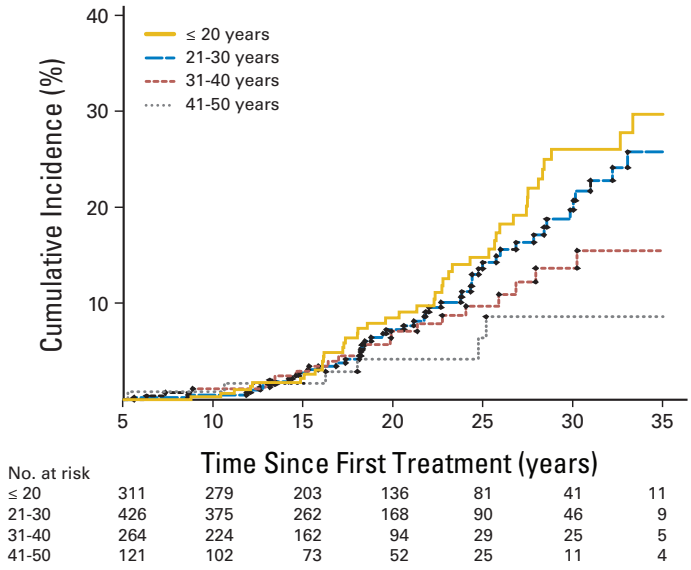

Figure 1.3: Absolute cumulative incidence of breast cancer in women treated with radiotherapy for HL. Risk of breast cancer is highest in patients treated at a younger age. Data are collected from a cohort of 1122 Dutch HL survivors all treated with radiotherapy between 1965-1995 (27).

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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