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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

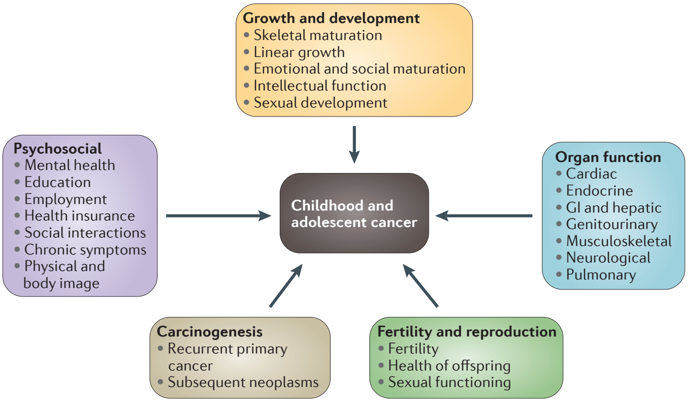

Figure 7.1: Range of health-related and quality of life outcomes among long-term survivors of childhood and adolescent cancers (21).

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.

Reference list

1. De Bruin ML, Sparidans J, Van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol* 2009 Sep 10,**27**(26), 4239-4246.
2. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003 Sep 15,**21**(18), 3431-3439.
3. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007 Mar 1,**109**(5), 1878-1886.
4. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst* 2007 Feb 7,**99**(3), 206-214.
5. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 2004 Aug 1,**22**(15), 3139-3148.
6. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003 Aug 20,**42**(4), 743-749.
7. van Leeuwen-Segarceanu EM, Bos WJ, Dorresteijn LD, et al. Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. *Cancer Treat Rev* 2011 Aug,**37**(5), 391-403.
8. Koornstra RH, Peters M, Donofrio S, van den Borne B, de Jong FA. Management of fatigue in patients with cancer - A practical overview. *Cancer Treat Rev* 2014 Feb 7.
9. Swerdlow AJ, Douglas AJ, Hudson GV, Hudson BV, Bennett MH, MacLennan KA. Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. *BMJ* 1992 May 2,**304**(6835), 1137-1143.
10. Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of Basal cell carcinoma: a report from the childhood cancer survivor study. *J Natl Cancer Inst* 2012 Aug 1,**104**(16), 1240-1250.
11. de Graaf FR, van Velzen JE, de Boer SM, et al. Non-invasive computed tomography coronary angiography as a gatekeeper for invasive coronary angiography. *Int J Cardiovasc Imaging* 2013 Jan,**29**(1); 221-228.
12. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. *Ann Intern Med* 2011 Mar 15,**154**(6), 413-420.
13. Rademaker J, Schoder H, Ariaratnam NS, et al. Coronary artery disease after radiation therapy for Hodgkin's lymphoma: coronary CT angiography findings and calcium scores in nine asymptomatic patients. *AJR Am J Roentgenol* 2008 Jul,**191**(1), 32-37.
14. Kupeli S, Hazirolan T, Varan A, et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. *J Clin Oncol* 2010 Feb 20,**28**(6), 1025-1030.

15. Girinsky T, M'Kacher R, Lessard N, et al. Prospective coronary heart disease screening in asymptomatic Hodgkin lymphoma patients using coronary computed tomography angiography: results and risk factor analysis. *Int J Radiat Oncol Biol Phys* 2014 May 1,**89**(1), 59-66.
16. Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol* 2007 Jan 1,**25**(1), 43-49.
17. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2007 Oct 2,**50**(14), 1343-1353.
18. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007 Sep 18,**50**(12), 1161-1170.
19. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1989 Jun,**79**(6), 1171-1179.
20. Collinson P. The role of cardiac biomarkers in cardiovascular disease risk assessment. *Curr Opin Cardiol* 2014 May 20, epub ahead of print.
21. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer* 2014 Jan,**14**(1), 61-70.
22. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol* 1986 May,**4**(5), 805-814.
23. Ganz PA, Bower JE. Cancer related fatigue: A focus on breast cancer and Hodgkin's disease survivors. *Acta Oncologica* 2007,**46**(4), 474-479.
24. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. *Cancer* 2011 Jun 15,**117**(12), 2779-2790.
25. Jager A, Sleijfer S, van der Rijt CC. The pathogenesis of cancer related fatigue: could increased activity of pro-inflammatory cytokines be the common denominator? *Eur J Cancer* 2008 Jan,**44**(2), 175-181.
26. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *J Clin Oncol* 2011 Sep 10,**29**(26), 3517-3522.
27. Sloan JA, de AM, Decker P, et al. Genetic variations and patient-reported quality of life among patients with lung cancer. *J Clin Oncol* 2012 May 10,**30**(14), 1699-1704.
28. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev* 2009,(1), CD006953.
29. Canellos GP. Is chemotherapy alone for early Hodgkin lymphoma an emerging therapeutic option? *Oncologist* 2009 Dec,**14**(12), 1167-1168.
30. Herbst C, Rehan FA, Brillant C, et al. Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review. *Haematologica* 2010 Mar,**95**(3), 494-500.

31. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol* 2014 Apr 20,**32**(12), 1188-1194.