Late cardiovascular and neurological complications in Hodgkin lymphoma survivors

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Thesis Utrecht University, faculty of Medicine, with summary in Dutch

Proefschrift Universiteit Utrecht, faculteit Geneeskunde, met een samenvatting in het Nederlands

ISBN:	978-90-9027537-6
Printed by:	PrintSupport4U, Meppel
Cover design and lay-out:	Roy Sanders
Photograph cover:	Casino in Constanţa, Roemenië, photograph by Geta Trofin

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Late cardiovasculaire en neurologische complicaties
bij succesvol behandelde patiënten met Hodgkin lymfoom
(*met een samenvatting in het Nederlands*)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op maandag 10 juni 2013 des middags te 2.30 uur

door

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geboren op 24 mei 1980 te Constanţa, Roemenië

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Het onderzoek dat in dit proefschrift beschreven wordt is mede mogelijk gemaakt door financiële steun van het IKMN (startsubsidie, project 2006.06; thans IKNL) en het Oncologie Centrum St. Antonius Ziekenhuis (AIOS project).

Dit proefschrift is mede tot stand gekomen door financiële steun van de Raad van Bestuur en Maatschap Interne Geneeskunde St. Antonius Ziekenhuis Utrecht/Nieuwegein, Chipsoft, Sanofi, Teva Nederland, Takeda.

Contents

1 General introduction

The incidence of Hodgkin lymphoma (HL) in Europe is 2.4 cases per 100,000 persons.[1] HL is yearly diagnosed in about 400 patients in the Netherlands.[2] The exact prevalence of HL survivors (HLS) in the Netherlands is unknown; in the Unites States there were approximately 175.000 HLS on January 1, 2009.[3] The International Agency for research on Cancer reported that 1568 HLS were alive in the Netherlands who were diagnosed with HL within 5 years of January 1, 2008.[2] Based on these figures we estimate the current number of long term (more than 10 years after diagnosis) HLS in the Netherlands to be a few thousand patients. Overall survival rates have improved dramatically over the last decades, attaining a mean of 90% (range 67-98%) 5-year survival for HL patients treated between 1980 and 2010 with regimens including modern chemotherapy regimens. [4] After 10 years of follow-up, mortality from HL decreases substantially, whereas many Hodgkin lymphoma survivors (HLS) still suffer from long-term complications of treatment.[5]

During the past decades, treatment modalities have been improved, not only resulting in better cure rates of HL, but also in less long-term toxicity. For patients with stage I or II HL, treatment has evolved from subtotal nodal irradiation (of the cervical, axillary, mediastinal hilar, para-aortic lymph nodes and of the spleen) to combined modality treatment with chemotherapy and less extensive radiotherapy.[6] However, there still is a major controversy [6-7] whether radiotherapy is really needed in combination with modern chemotherapy regimens in non-bulky early stage HL. Monotherapy with chemotherapy has also been shown to result in high overall survival rates in this group.[8] Furthermore, radiotherapy has been associated with most long-term complications in HL.[9] Therefore, current practice guidelines from the National Comprehensive Cancer Network (NCCN) describe two alternative options for the treatment of patients with limited stage HL: abbreviated chemotherapy plus involved-field radiation therapy (IFRT) or chemotherapy alone with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD).[10] Currently, some trials are investigating the role of interim positron emission tomography (PET) imaging, following 2 or 3 cycles of chemotherapy in the response-adapted tailoring of treatment (GHSG -HD16, EORTC-GELA H10 and the RAPID Trial).[11] Radiation remains a critical component of the treatment of bulky early stage HL, since these

patients are at greater risk for relapse.[12] For advanced stage HL there is consensus that combination chemotherapy is the standard initial therapy. The chemotherapy regimen with the highest rate of response and least toxicity is still a matter of debate.[13-14] The role of consolidation radiotherapy after chemotherapy induction for advanced stage HL is controversial and the decision to proceed with adjuvant radiation after chemotherapy should be individualised. [15-17] Especially HL patients in partial remission or presenting with bulky mediastinal disease (> 10cm or > 1/3 of mediastinum) benefit from adjunctive radiotherapy to regions with residual disease or to the initial bulky site.[15-17]

The choice for a therapeutic regimen in HL patients is also influenced by the long term complications of treatment. Older chemotherapy regimens have been replaced by newer combinations because of the high rate of secondary leukaemia which were observed years after treatment (especially in patients treated with the alkylating agent mechlorethamine in the MOPP scheme). Many patients received extended field radiotherapy like subtotal nodal irradiation (STNI) and mantle field irradiation (STNI without radiotherapy to the para-aortal lymph nodes and the spleen). This type of irradiation was abandoned at the end of the 1990's because less extensive field radiotherapy in combination with chemotherapy resulted in similar curation rates with fewer side effects.[18] Currently involved field radiotherapy (treatment to the entirety of a lymphoid region) is the standard, with efforts being made to narrow the radiation fields even more, to involved node radiotherapy.[19] Furthermore, radiation doses were lowered from over 40 Gy to 20-30 Gy in combination with chemotherapy.[20] Limiting the exposure of normal tissues to the damaging effect of radiotherapy was the main reason for these adjustments.

Over time, evidence became available that radiotherapy is associated with adverse effects, especially in long time survivors of extensive field radiotherapy.[21] Secondary malignancies in tissues situated within the radiation fields (breast, lung, oesophagus, thyroid) have been the leading cause of death in long term survivors of HL.[5] Numerous studies describing the risk of secondary malignancies and guidelines about screening for these cancers are available.[22-25]

Cardiovascular diseases (CVD) are the most prevalent *non-malignant* cause of death in HLS. [5] There are many studies describing the incidence of symptomatic cardiovascular end points like stroke, myocardial infarction, valvular disorders, congestive heart failure, pericardial disease and conduction abnormalities.[9, 26-32] However, data on pre-clinical indicators of these disorders are scarce [33-35]. No uniform guidelines are available for screening HLS for CVD.[22-24]

Currently, many screening modalities are under investigation for the detection of pre-clinical CVD in high-risk populations like patients with diabetes, hypertension, hypercholesterolemia, renal dysfunction etc.[36-41] Arterial stiffness parameters have been proven to adequately predict the occurrence of cardiovascular disease in several high risk populations.[36] The aortic pulse wave velocity measured between the carotid and femoral arteries (PWVcf) is considered the 'gold-standard' indicator of arterial stiffness.[42] Recently, a meta-analysis of 17 studies demonstrated a correlation between PWVcf and clinical outcomes. Patients with a high PWVcf have a relative risk of 2.26 of developing a cardiovascular event.[36] For HLS treated with mediastinal radiotherapy, the PWVcf would be of use to determine if aortic stiffening has occurred in consequence to radiotherapy. However, for HLS treated with radiotherapy to the cervical lymph nodes only, PWVcf would not be of use. Common carotid artery (CCA) distensibility coefficient (DC) is another indicator of arterial stiffness which is probably more suitable to use in this subgroup of HLS.[43] DC was also shown to be independently related to the occurrence of stroke and TIA in a high risk population for CVD.[43] In HLS treated with only chemotherapy, both indicators of arterial stiffness can be used to assess the risk of cardiovascular disease. Advantages of these parameters are the non-invasive way of investigation and the relative ease of use of the techniques. Furthermore, lowering blood pressure has been shown to be associated with a decrease in PWVcf, independent of blood pressure decrease.[44-45] Also DC improved after a treatment regimen combining a statin, vitamin E and homocysteine lowering in patients with chronic kidney disease.[46] Whether lowering arterial stiffness itself or lowering the blood pressure and optimising other CVD risk factors will lead to improved long-term outcomes, is not clear.

Indicators of atherosclerosis like increased intima media thickness (IMT) of the CCA, the presence of plaque in the CCA and increased coronary artery calcium (CAC)-score have also been used as predictors of CVD in asymptomatic patients.[37-38, 47] In a recent meta-analysis of almost 46,000 patients, increase in CCA IMT was associated with greater risk of myocardial infarction and stroke.[48] However, the addition of IMT measurements to the Framingham Risk Score was associated with small improvement in risk prediction of myocardial infarction or stroke.[48] Arterial plaque can also be detected by ultrasound during the measurements of CCA IMT. The combination of plaque and increased IMT seems to define the group with the highest risk of developing CVD.[38] Since HLS have been shown to have an increased risk of developing stroke and transient ischemic attacks (TIA)[49], the yield of screening HLS for carotid artery disease should be investigated. It is not being recommended to use screening ultrasounds of the CCA in asymptomatic patients because of the relatively low excess cases of stroke and TIA in HLS,[49] however no research has been conducted yet to confirm these recommendations. Furthermore, timely recognition of carotid artery disease in HLS results in much better outcomes, since all patients with carotid artery disease presenting with a stroke were fatal or resulted in permanent hemiparesis.[50]

Since myocardial infarction was recognised as a frequent complication of mediastinal radiotherapy, several studies have been published on screening methods to detect asymptomatic coronary artery disease (CAD). In HLS stress-induced ischemia detection (by echography, electrocardiography or scintigraphy) has demonstrated disappointing diagnostic characteristics in the few studies in which they were compared to the gold-standard: coronary angiography.[33, 51-53] Non-invasive modern imaging techniques like computed tomography (CT) for the measurement of CAC-score, CT- and MRI-angiography have been used since the 1990's for the detection of CAD. The latter two methods are mainly used for research purposes for the detection of CAD, the broader applicability of research centre results is not yet established.[54] CAC-score measurements however, are available on a large scale. CAC-score has been shown to be predictive of both coronary artery stenosis of more than 50% and cardiovascular events as well.[55-57] Furthermore,

CAC-scoring has the advantage of being relatively cheap, the radiation exposure being low and not requiring intravenous contrast fluid. Despite the potential benefits of CAC screening, there are a number of limitations to CAC screening which cause disagreement about its value.[58] The relative low-population risk in asymptomatic patients referred for CAC-score measurements means that a clinical event will only occur in a small number of patients with coronary calcifications. It has not been proven that initiating pharmacologic treatment in asymptomatic patients with high CAC-scores improves outcome.[59-61] The cost-effectiveness has not been established since additional tests are frequently required to identify the degree and significance of CAD.[62] Mediastinal radiotherapy has been recognised as a risk factor for the development of CAD [63], however no trials performed so far into the prognostic value of CAC-scores have included HLS. Therefore the value of CAC screening in HLS remains unknown. For this group of patients screening for CAD has been advocated by experts in the field. [9, 29, 64] CAC screening can be a suitable method when looking at the advantages presented above and regarding the guidelines of the American College of Cardiology/ American Heart Association which recommend CAC screening in populations at intermediate (10-20%) ten year risk or CAD.[65]

Other less prevalent, but very invalidating, late effects of HL treatment like neurological complications have also received little attention in the literature.[66-67] HLS treated with radiotherapy to the neck often complain of a painful neck or a tired feeling in the neck muscles. [66-67] Physicians treating HLS often recognize patients treated with mantle field radiotherapy by their thin neck and sometimes even the necessity to support the head with their hand after sitting for a while. Since the etiology of muscle damage after radiotherapy is largely unknown, treating physicians do not know how to manage the complaints of these patients.[68]

The desire of improving long-term survival of Hodgkin lymphoma patients by optimizing treatment modalities and decreasing long-term complications has led to the actual interest in the development of screening strategies, not only for secondary malignancies but also for neuro- and cardiovascular disorders. For example, the nationwide Dutch consortium **BETTER** (**B**etter care after Hodgkin lymphoma: **E**val-

uation of long-**T**erm **T**reatment **E**ffects and screening **R**ecommendations) has begun an initiative of uniformly screening Hodgkin lymphoma survivors on late effects of treatment. Data from our cohort HLS will contribute to a better understanding of the prevalence of subclinical cardiovascular and neurological late effects. Furthermore, identification of risk factors for these late effects will facilitate the identification, closer monitoring and treatment of individuals at high risk of developing symptomatic disease.

Outline of the thesis

The aim of this thesis is to investigate subclinical cardio- and neurovascular complications of treatment in Hodgkin lymphoma survivors (HLS). Preclinical cardiac and vascular disorders are investigated in a cohort of 82 HLS and 40 age and gender matched control subjects. Furthermore, neck muscle complaints are studied in a subgroup of 12 HLS previously treated by mantle field radiotherapy.

In **Chapter 2** a review of the available literature on cardiovascular complications of radiotherapy is presented followed by a suggestion for a cardiovascular screening program. This review focuses on coronary artery disease, valvular disorders, pericardial disease, cardiomyopathy, arrhythmias and conduction system disease, carotid artery disease and other vascular pathology. For the two most prevalent disorders (coronay artery disease and valvular disorders) the rationale of screening, the risk groups among the HLS who should be closely monitored, the best timing of initiation of screening and screening intervals and the best screening modalities are assessed.

In **Chapter 3** arterial stiffness is described for the first time in patients treated with radiotherapy. The carotid-femoral pulse wave velocity (PWVcf) and the distensibility coefficient (DC) of the common carotid artery are used as markers of arterial stiffness. HLS treated with radiotherapy to the aorta and carotid artery respectively are compared to HLS treated without radiotherapy and to healthy controls. Patient- and HL therapy related risk factors for arterial stiffening are studied.

The PWVcf is nowadays considered the 'gold-standard' indicator of arterial stiffness. Various measuring techniques have been used to estimate the PWVcf. However, there is no consensus about which measuring method is the most valid and reliable. In **chapter 4,** two instruments measuring PWVcf are compared: the Sphygmocor versus the Vicorder. The SphygmoCor is a device that has been extensively used in clinical studies for a long time, however it is a time consuming device which requires some experience from the technician using it. The Vicorder is a new device, recently approved by the FDA, which is supposed to be easy in use and less operator-dependent.

Radiotherapy of the neck has been associated with a higher risk of stroke and TIA in HLS.[49] Carotid artery disease and cardiac emboli have been suggested as causes of stroke and TIA. Preclinical indicators of atherosclerosis are described in **chapter 5.** Intima media thickness (IMT) of the common carotid artery and occurrence of plaque in the neck arteries are compared between HLS irradiated on the neck, HLS treated without radiotherapy on the neck and healthy controls.

Coronary artery disease detection methods have been extensively investigated in HLS.[33-34, 51-53, 69-70] A new method, recently introduced in cardiac practice, CAC-score measurement, is evaluated in **chapter 6.** 75 HLS were measured and classified as having high-risk for developing CAD when exceeding the 75th percentile for age and sex in the normal population and low-risk when found to have a CAC-sore of 0.

Chapter 7 describes the results of screening HLS with echocardiography. Assessment of valvular disorders is presented and risk factors for developing these disorders are investigated. The aim of this chapter is to incorporate cardiac disease screening into a comprehensive screening program.

In **chapter 8** the findings of neck muscle ultrasound, nerve conduction studies and needle electromyography are described in 12 HLS treated with mantle field radiotherapy. The aim of this study is to gain more insight in the pathophysiology and the clinical picture of neck muscle atrophy and weakness. Furthermore suggestions are given for the management of these complaints.

The findings of the above mentioned studies are summarized in **chapter 9.**

Finally, in **chapter 10** the obtained results are discusses and placed into perspective of the current literature. Suggestions are presented for a screening program for the detection of cardiovascular disorders in HLS and for further research on this subject.

References

1. Sant M, Allemani C, Tereanu C*, et al.* Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood* 2010;116:3724-3734.
2. Ferlay J SH, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. *Lyon, France: International Agency for Research on Cancer; 2010. Available from http://globocan.iarc.fr, accessed on 10/01/2013*.
3. http://seer.cancer.gov/statfacts/html/hodg.html?statfacts_page=hodg.html&x-=12&y=15.
4. Moccia AA, Donaldson J, Chhanabhai M*, et al.* International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol* 2012;30:3383-3388.
5. Aleman BM, van den Belt-Dusebout AW, Klokman WJ*, et al.* Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003;21:3431-3439.
6. Meyer RM, Hoppe RT. Point/counterpoint: early-stage Hodgkin lymphoma and the role of radiation therapy. *Blood* 2012;120:4488-4495.
7. Yahalom J. Don't throw out the baby with the bathwater: on optimizing cure and reducing toxicity in Hodgkin's lymphoma. *J Clin Oncol* 2006;24:544-548.
8. Meyer RM, Gospodarowicz MK, Connors JM*, et al.* ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med* 2012;366:399-408.
9. Aleman BM, van den Belt-Dusebout AW, De Bruin ML*, et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878-1886.
10. Hoppe RT, Advani RH, Ai WZ*, et al.* Hodgkin lymphoma. *J Natl Compr Canc Netw* 2011;9:1020-1058.
11. clinicaltrials.gov.
12. Hoppe RT, Coleman CN, Cox RS*, et al.* The management of stage I--II Hodgkin's disease with irradiation alone or combined modality therapy: the Stanford experience. *Blood* 1982;59:455-465.
13. Bauer K, Skoetz N, Monsef I*, et al.* Comparison of chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for patients with early unfavourable or advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev* 2011:CD007941.
14. Borchmann P, Trelle S, Rancea M*, et al.* First Line Treatment of Advanced Stage Hodgkin Lymphoma with Six Cycles of $BEACOPP_{escalated}$ Results in Superior Overall Survival Compared to ABVD: Results of a Network Meta-Analysis Including 10,011 Patients. 54th ASH Annual Meeting and Exposition. Atlanta, GA.; 2012.

15. Johnson PW, Sydes MR, Hancock BW*, et al.* Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). *J Clin Oncol* 2010;28:3352-3359.
16. Gordon LI, Hong F, Fisher RI*, et al.* Randomized Phase III Trial of ABVD Versus Stanford V With or Without Radiation Therapy in Locally Extensive and Advanced-Stage Hodgkin Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol* 2012.
17. Aleman BM, Raemaekers JM, Tomisic R*, et al.* Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2007;67:19-30.
18. Ferme C, Eghbali H, Meerwaldt JH*, et al.* Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med* 2007;357:1916-1927.
19. Koeck J, Abo-Madyan Y, Lohr F*, et al.* Radiotherapy for early mediastinal Hodgkin lymphoma according to the German Hodgkin Study Group (GHSG): the roles of intensity-modulated radiotherapy and involved-node radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;83:268-276.
20. Engert A, Plutschow A, Eich HT*, et al.* Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010;363:640-652.
21. Ng AK, Li S, Neuberg D*, et al.* Long-term results of a prospective trial of mantle irradiation alone for early-stage Hodgkin's disease. *Ann Oncol* 2006;17:1693-1697.
22. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, 2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
23. Children's Oncology Group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, 2008. http://www.guidelines.gov/summary/summary.aspx?ss=15&doc_id=10772&nbr=5600.
24. Ng A, Constine LS, Advani R*, et al.* ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer* 2010;34:211-227.
25. Ng AK, Bernardo MV, Weller E*, et al.* Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. *Blood* 2002;100:1989-1996.
26. Boivin JF, Hutchison GB, Lubin JH*, et al.* Coronary artery disease mortality in patients treated for Hodgkin's disease. *Cancer* 1992;69:1241-1247.
27. Carlson RG, Mayfield WR, Normann S*, et al.* Radiation-associated valvular disease. *Chest* 1991;99:538-545.
28. Handa N, McGregor CG, Danielson GK*, et al.* Coronary artery bypass grafting in patients with previous mediastinal radiation therapy. *J Thorac Cardiovasc Surg* 1999;117:1136-1142.

29. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
30. King V, Constine LS, Clark D*, et al.* Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1996;36:881-889.
31. Kleikamp G, Schnepper U, Korfer R. Coronary artery and aortic valve disease as a long-term sequel of mediastinal and thoracic irradiation. *Thorac Cardiovasc Surg* 1997;45:27-31.
32. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ*, et al.* Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. *Radiother Oncol* 1999;51:35-42.
33. Heidenreich PA, Hancock SL, Lee BK*, et al.* Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743-749.
34. 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* 2009.
35. Wethal T, Lund MB, Edvardsen T*, et al.* Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. *Br J Cancer* 2009;101:575-581.
36. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318-1327.
37. Lorenz MW, Markus HS, Bots ML*, et al.* Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007;115:459-467.
38. Nambi V, Chambless L, Folsom AR*, et al.* Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010;55:1600-1607.
39. Becker A, Leber A, Becker C*, et al.* Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. *Am Heart J* 2008;155:154-160.
40. Goodman WG, Goldin J, Kuizon BD*, et al.* Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478-1483.
41. Raggi P, Shaw LJ, Berman DS*, et al.* Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;43:1663-1669.
42. Laurent S, Cockcroft J, Van Bortel L*, et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-2605.

43. Dijk JM, van der Graaf Y, Grobbee DE, *et al.* Increased arterial stiffness is independently related to cerebrovascular disease and aneurysms of the abdominal aorta: the Second Manifestations of Arterial Disease (SMART) Study. *Stroke* 2004;35:1642-1646.
44. Ichihara A, Hayashi M, Koura Y, *et al.* Long-term effects of intensive blood-pressure lowering on arterial wall stiffness in hypertensive patients. *Am J Hypertens* 2003;16:959-965.
45. Karalliedde J, Smith A, DeAngelis L, *et al.* Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 2008;51:1617-1623.
46. Veringa SJ, Nanayakkara PW, van Ittersum FJ, *et al.* Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on arterial compliance and distensibility in patients with mild-to-moderate chronic kidney disease. *Clin Nephrol* 2012;78:263-272.
47. Raggi P, Callister TQ, Cooil B, *et al.* Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850-855.
48. Den Ruijter HM, Peters SA, Anderson TJ, *et al.* Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *Jama* 2012;308:796-803.
49. De Bruin ML, Dorresteijn LD, van't Veer MB, *et al.* Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst* 2009;101:928-937.
50. Patel DA, Kochanski J, Suen AW, *et al.* Clinical manifestations of noncoronary atherosclerotic vascular disease after moderate dose irradiation. *Cancer* 2006;106:718-725.
51. 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;22:3139-3148.
52. Constine LS, Schwartz RG, Savage DE, *et al.* Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1997;39:897-906.
53. Girinsky T, Cordova A, Rey A, *et al.* Thallium-201 scintigraphy is not predictive of late cardiac complications in patients with Hodgkin's disease treated with mediastinal radiation. *Int J Radiat Oncol Biol Phys* 2000;48:1503-1506.
54. Mavrogeni S, Papadopoulos G, Douskou M, *et al.* Magnetic resonance angiography is equivalent to X-ray coronary angiography for the evaluation of coronary arteries in Kawasaki disease. *J Am Coll Cardiol* 2004;43:649-652.
55. Kondos GT, Hoff JA, Sevrukov A, *et al.* Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107:2571-2576.

56. Pletcher MJ, Tice JA, Pignone M*, et al.* Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med* 2004;164:1285-1292.
57. Haberl R, Becker A, Leber A*, et al.* Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001;37:451-457.
58. Mozaffarian D. Electron-beam computed tomography for coronary calcium: a useful test to screen for coronary heart disease? *Jama* 2005;294:2897-2901.
59. Arad Y, Spadaro LA, Roth M*, et al.* Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005;46:166-172.
60. Raggi P, Davidson M, Callister TQ*, et al.* Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* 2005;112:563-571.
61. Schmermund A, Achenbach S, Budde T*, et al.* Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. *Circulation* 2006;113:427-437.
62. O'Malley PG, Greenberg BA, Taylor AJ. Cost-effectiveness of using electron beam computed tomography to identify patients at risk for clinical coronary artery disease. *Am Heart J* 2004;148:106-113.
63. Galper SL, Yu JB, Mauch PM*, et al.* Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. *Blood* 2011;117:412-418.
64. 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;99:206-214.
65. Greenland P, Bonow RO, Brundage BH*, et al.* ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;49:378-402.
66. Fossa SD, Holte H, Holmen MM*, et al.* [Long-term effects after mantle field radiotherapy for Hodgkin's lymphoma]. *Tidsskr Nor Laegeforen* 2005;125:41-44.

67. Johansson AS, Erlanson M, Lenner P*, et al.* [Late side-effects are common after treatment of Hodgkin's disease. Muscular atrophy following radiotherapy is a neglected risk]. *Lakartidningen* 1998;95:44-47.
68. Furby A, Behin A, Lefaucheur JP*, et al.* Late-onset cervicoscapular muscle atrophy and weakness after radiotherapy for Hodgkin disease: a case series. *J Neurol Neurosurg Psychiatry* 2010;81:101-104.
69. Andersen R, Wethal T, Gunther A*, et al.* Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. *Am J Cardiol* 2010;105:149-152.
70. 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;191:32-37.

2 Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease

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Cancer Treatment Reviews 2011; 37(5):391-403

Abstract

Long term prognosis of Hodgkin lymphoma (HL) survivors is affected by late toxicity of radiotherapy and chemotherapy. Cardiovascular complications of radiotherapy have been shown to have a great impact on the long term survival. The aim of this review is to summarize the available data on different screening modalities for cardiovascular disease and to suggest a screening program.

Patients older than 45 years at HL diagnosis should be screened for coronary artery disease (CAD) starting five years after mediastinal radiotherapy; they are at increased risk of pre-existent atherosclerosis which can be accelerated by radiotherapy. Screening for CAD should start 10 years after radiotherapy in younger patients. The best screening modality for CAD is subject of discussion, based on the latest studies we suggest screening by Coronary artery calcium score measurements or CT-angiography. Valvular disorders should be looked for by echocardiography starting 10 years after radiotherapy. Electrocardiograms should be performed at each cardiovascular screening moment in order to detect arrhythmia's or conduction abnormalities. We suggest repeating these screening tests every five years or at onset of cardiovascular complaints; patients should be extensively instructed about signs and symptoms of cardiovascular disease. Furthermore traditional risk factors for cardiovascular disease should be carefully monitored and treated. We suggest determining a cardiovascular risk profile at diagnosis of HL in patients older than 45 years. In case of a high risk, treating HL without RT should be considered.

Introduction

Hodgkin lymphoma (HL) accounts for approximately 0.6% of all cancers diagnosed in the developed world annually, with 8220 new cases and about 1350 deaths due to HL in the United States annually.[1] Hodgkin lymphoma survivors (HLS) are at increased risk of developing late cardiovascular complications. The course of these cardiovascular disorders is often asymptomatic even in the presence of severe disease.[2] Moreover, symptoms are often misinterpreted because of young age and lack of other cardiovascular risk factors (RF).[3]

There are no guidelines for comprehensive cardiovascular screening programs in HLS. Different brief suggestions have been made by different organizations, all without high level of evidence.[4-6] The most recently updated guidelines, the National Comprehensive Cancer Network (NCCN) Clinical Guidelines do recommend annual screening and 'aggressive management of cardiovascular risk factors' and a baseline 'stress test/echocardiogram' at 10 years. However there are no recommendations on the frequency of screening for coronary artery disease (CAD) or valvular disease. Furthermore the only article where this guideline is based on was published in 2005[7] and some important studies have been published since.[2, 8, 9] The relative low numbers of HLS and the latency in the development of cardiovascular sequelae have hampered large studies into the costs and benefits of a screening program for cardiovascular disorders.[10]

The purpose of this review is to summarize the available data on cardiovascular events in HLS treated by radiotherapy (RT) and to suggest a screening program. This review focuses on CAD, valvular disorders, pericardial disease, cardiomyopathy, arrhythmias and conduction system disease, carotid artery disease and other vascular pathology. Most information is available about CAD and valvular disorders; for these disorders, we address the following items: why screening, whom to screen, when to start screening and how to screen.

Coronary artery disease (CAD)

Survivors of Hodgkin lymphoma who were treated with mediastinal RT face significantly increased risks of premature CAD. Many studies showed that the risk of a fatal myocardial infarction (MI) in HLS is 2.2 to 7.6-fold greater than in the general population.[7, 11-15] Aleman reported a cumulative incidence for myocardial infarction of 12.9% by 30 years

after mediastinal irradiation.[8] They reported a standardized incidence ratio of 3.6 for MI, with 357 excess cases per 100,000 person years. Screening for asymptomatic CAD in HLS has been advocated by experts in the field.[8, 12, 13, 15-17]

1. Why screening?

Patients with radiation-induced CAD are often asymptomatic even in the presence of severe CAD. This is best illustrated by screening studies in which severe CAD confirmed by coronary angiography (CAG) is diagnosed in asymptomatic HLS (Table 1).[2, 18, 19] In the largest study of 294 patients the prevalence of asymptomatic severe CAD for which revascularization was required was 3.1%.[2] Two smaller studies showed a prevalence of 4.2% (1/24 HLS) [18] and 1.7% (2/119 childhood HLS).[19] In other reports no signs of ischemia during the screening of asymptomatic patients were documented, however these studies are only describing a small group of patients or have a short follow-up (FU) interval (Table 1).[20-24]

The clinical presentation of RT-induced CAD is comparable to the general population and mainly consists of angina pectoris (AP), (fatal) acute myocardial infarction (AMI) or sudden death.[3, 25-32] However, typical AP complaints are the initial presentation of CAD in a smaller proportion of HLS (22%)[25] compared to the Framingham population (45%).[33] It is conceivable that patients with RT-induced CAD remain asymptomatic for a long time because of RT-related nerve impairment or reduced exercise tolerance.[31] Not recognizing or misdiagnosing of AP complaints can cause substantial delays, especially in young HLS without other risk factors for CAD.[3]

Patients with significant CAD can present with symptoms other than AP, because patients with radiation-induced cardiac disease often have more concomitant disorders. [32, 34-36] In a case series of 15 patients surviving mediastinal RT and suffering from severe CAD, only 8 had typical angina; 7 patients presented with dyspnea, weakness or heart failure. [37] In a similar study, 10 of the 15 patients presented with AP, three with AMI, one with syncope and one with dyspnea. In these patients other cardiac involvement was demonstrated (8 had valvular disease, 3 constrictive pericarditis, 4 complete heart block).[38]

Asymptomatic patients with severe CAD should be identified in order for timely revascularization to be performed.[38] The outcomes of coro-

nary artery bypass graft (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in RT-induced CAD do not seem inferior in HLS as compared to the general population: all 12 HLS were alive at a mean of two years FU after CABG.[3] Combined surgery for other cardiovascular disorders is often needed. Handa et al recommend a careful planning of interventions. They describe the follow-up of CABG in 47 patients treated with mediastinal RT.[39] In 12 of 21 patients who were assessed by echocardiography after a mean interval of 5.9 years from CABG, significant valvular disease was seen; two patients required a valvular surgery and two died of congestive heart failure.

Follow-up of asymptomatic HLS with CAD who do not require immediate revascularization therapy is necessary.[2, 34] In animal models it has been shown that irradiation accelerated the development of atherosclerosis.[40] There is, however, no evidence from intervention studies regarding the benefit of any treatment altering the natural history in asymptomatic HLS with CAD. Therefore close monitoring and cardiovascular risk management has been advocated in these patients.[4, 41]

2. Whom to screen?

Patients with concomitant traditional RF

Although several studies suggest that CAD develops only in HLS with more than one classical RF (hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, positive family history of CAD) [17, 25, 26, 29], other studies also showed an increased risk in subjects without classical RF. When describing irradiated patients with CAG or CT-angiography proven CAD, 41/67 patients (61%) had no traditional RF. [19, 31, 32, 34, 38, 42] Therefore the absence of traditional RF cannot be used as a criterion to exclude patients from screening.

Glanzman et al found that the presence of traditional RF in HLS conferred a 2.36 relative risk of ischemic heart disease compared with the expected rate among the general population with the same RF. This suggests that traditional RF are more hazardous among HLS than among the general population.[26] HLS with traditional RF have been shown to develop CAD earlier and at a younger age than HLS without these RF.[3] These findings demonstrate the importance of vigilant evaluation and treatment of traditional RF in HLS.[9, 43] Chen et al developed a decision-analytic model to evaluate lipid screening in a hypothetical cohort of 30-year-old HLS who survived 5 years after mediastinal RT.

Table 1 Screening studies describing CAD in HLS. CAC coronary artery calcium; CAD coronary artery vors; MI myocardial infarction; RT radiotherapy; SD standard deviation.

Study	Nr. of HLS screened	Median age at treatment (SD/range)	Median FU in years (SD/range)	Treatment type	Number of HLS with CAD
Heidenreich[2] 2007	294	42 (9)	mean: 15 (7)	All mediastinal RT median 44Gy (35-55 Gy). 56% CT.	- 31/294 (11%), - 9/294 (3.1%) needing revascularisation
Gustavsson[18] 1990	24	38 (21-45)	15 (4-20)	All mantle field RT mean 40Gy (35-43 Gy). No CT.	1/24 (4.2%)
Kupeli[19] 2009	119	7 (2-18)	12 (2-31)	92% CT+RT (mediastinal RT in 54%). 8% only CT.	- 19/119 (16%), - 2/119 (1.7%) needing revascularisation
Pohjola-Sintonen[20] 1987	28	32 (12-38)	9 (5-14)	All mediastinal RT mean 38Gy (34-47 Gy). No CT.	- 3/28 (11%), - 2/28 (7%) needing revascularisation
Adams[56] 2004	48	16.5 (6-25)	14 (6-25)	All mediastinal RT, mean 40Gy (27-52 Gy). 44% CT.	2/48 (4%): - 1 old q-wave MI, - 1 exercise induced ischemia
Gottdiener[22] 1983	25	28	11 (5-15)	All mediastinal RT (all but one ≤40Gy). No CT.	2/25 (8%)
Andersen[10] 2010	47	27 (6)	22 (3)	All mediastinal RT, mean 41 ± 2Gy. 74% CT.	- 7/47 (15%) had pre-existent CAD - 5/40 (13%) CAC score >200
Glanzmann[26] 1998	144	30 (4-65)	14 (2-32)	All RT, between 30-45Gy. CT in unknown number.	5/144 (3%)
Kreuser[21] 1993	49	35 (15-58)	5 (2-10)	Mediastinal RT in 63% (20 or 30Gy). All CT.	0
Pihkala[23] 1995	30	9 (2-16)	7 (2-13)	All mediastinal RT mean 26Gy (10-51 Gy). 93% CT.	0
Watchie[24] 1987	57	30 (6)	Mean: 5 (4)	88% mediastinal RT (43-55Gy). 47% CT.	0

disease; CAG coronary angiography; CT chemotherapy; FU follow-up; HLS Hodgkin Lymphoma survi-

Mean time until CAD developed in years (SD/range)	Screening modalities	Remarks
21 (6)	Stress echocardiography, treadmill testing, radionuclide perfusion imaging. HLS with a positive stress test were advised to undergo CAG.	HLS who already had CAD were excluded. In the whole cohort of 972 HLS, 14/33 HLS died from MI within 10 years after RT. The patients with CAD were asymptomatic
19	Exercise test and myocardial scintigraphy.	The patient with CAD was asymptomatic
14 (5-31)	Computed tomography-angiography. One patient with significant stenosis underwent CAG, the other refused CAG.	The patients with CAD were asymptomatic
9 (6-11)	Exercise test confirmed by CAG in 2 patients. In the 3rd patient a thallium scintigraphy revealed no evidence of ischemia.	The 3 patients with signs of ischemia were not asymptomatic, they complained of angina pectoris or dyspnea
Data is not presented in the article.	Exercise test.	No confirmation by CAG was available; there is no further description of the 2 patients with documented ischemia on screening.
5yr in one patient, is not described in the other.	Radionuclide cineangiography at rest and during exercise in 15 patients.	No subcarinal shielding was used. The 2 patients with wall motion abnormalities had already CAD disease previously demonstrated on CAG
Data is not presented in the article.	Coronary artery calcium score.	No subcarinal shielding was used. No confirmation by CAG was available. 5 HLS with CAC score > 200 were asymptomatic.
Data is not presented in the article.	Exercise test.	No confirmation by CAG was available, there is no further description of the 2 patients with documented ischemia on screening.
-	Exercise test.	
-	Exercise test.	Only 7 patients were treated were HLS the other received RT for leukemia, non-Hodgkin lymphoma, Wilm's tumor.
-	Exercise test.	

They demonstrated that that lipid screening every 3 years would be the most cost-effective strategy in this population. Furthermore, when statin therapy is initiated in screen-positive HLS, survival was shown to be improved.[44] The optimal screening interval for hypertension or diabetes mellitus has not been established. Different guidelines based on expert opinion recommend yearly measurements of blood pressure and fasting blood glucose.[4, 5] When hypercholesterolemia, hypertension or diabetes mellitus are diagnosed, we recommend treating these disorders according to the appropriate guidelines,[45-47] considering mediastinal RT as a risk factor.

Patients treated with higher radiation doses

Most studies in adult HLS report CAD in patients who received more than 35 Gy radiation to the heart (Table 2). Lower doses have only been given in adults in since the late 1990's.[2] Long term follow-up data are therefore not available for lower radiation doses. Most data on CAD in HLS treated with a lower radiation dose are from childhood HLS.[48] In a

Table 2 Cohort studies describing CAD in HLS. CAD coronary artery disease; CT chemotherapy; HR hazard ratio; (A)MI acute myocardial infarction; RT radiotherapy.

Study	Nr. of HLS	Median age at treatment (range)	Median FU in years (range)	Treatment type	Number of HLS with CAD
Aleman[8] 2007	1 474	26 (max. 40yr, 111 HLS <16yr)	19 (min 5yr)	84% mediastinal RT (30-36Gy when RT+CT, 40Gy if RT only). 72% CT.	- 134/1474 (9%) angina pectoris - 102/1474 (7%) AMI
Swerdlow[13] 2007	7 033	60% <35yr 40% ≥35yr	10	49% supradiafragmatic RT. 99% CT.	166/7033 (2%) deaths from MI
Hull[17] 2003	415	25 (4-75)	11 (2-36)	95% mediastinal RT, mean 33 Gy (10-7Gy). 62% CT	42/415 (10%) CAD
Kupeli[19] 2009	119	7 (2-18)	12 (2-31)	92% CT+RT (mediastinal RT in 54%). 8% only CT.	19/119 (16%) asymptomatic CAD on CTA.
Hancock[48] 1993	635	15 (2-20)	10	91% mediastinal RT (71% ≥40 Gy, 15% ≤30 Gy). 63% CT.	- 7/635 (1%) deaths from AMI - 6/635 (1%) nonfatal CAD
Mulrooney[49] 2009	14 358	6 (0-20)	20 (5-27)	71% cardiac RT (34% <5 Gy, 16% 5-34 Gy, 7% 35 Gy).80% CT	101/14 358 (1%) first MI

recent large cohort study (n=14 358) in childhood cancer survivors, a radiation dose of 15-34 Gy was associated with a hazard ratio (HR) for MI of 2.4 (p= 0.01) in comparison with patients treated without RT (Table 2).[49] Patients treated with radiation dose of 5-15 Gy did not have an increased risk when compared to patients treated without RT.[49] Küpeli et al found CT-angiography proven CAD in 19 out of 119 childhood HLS; in multivariate analysis patients receiving > 20 Gy mediastinal RT had a 6.8 (95% CI, 1.6-28.8) times increased risk of developing CAD than patients treated without RT.[19] Considering these results it seems reasonable to consider mediastinal radiation above 15 Gy as a RF for the development of CAD. There is however growing evidence of a linear dose-response relation for CAD, as demonstrated in Japanese atomic bomb survivors.[50]

Patients treated with both chemotherapy and radiotherapy

There are unfortunately no long-term follow-up results describing the incidence of CAD in randomized controlled trials (RCT's) comparing

CTA Computed tomography-angiography; FU follow-up; HLS Hodgkin Lymphoma survivors;

Median interval until CAD developed in years (range)	Relative risk/hazard ratio associated with different RT doses	Remarks
- 21 (5-37) for angina pectoris - 19.5 (7-37.5) for AMI	Data on RT dose for individual patients was not collected	Patients with a prior history of CVD before HL diagnosis were excluded. CVD occurring within 5 years after HL diagnosis were also excluded.
57% of events occurred <10 yrs after treatment	Data on RT dose for individual patients was not presented	64% of deaths from MI occurred when age at 1st treatment was ≥45yrs (only 25% were ≥45yrs at treatment).
9 (1-32)	CAD developed in HLS treated with 25-42Gy (mean 36), not different from total HLS group	
14 (5-31)	HLS receiving >20 Gy had an 6.8 times increased risk of CAD compared to ≤ 20Gy	
- 14 (6-22) for deaths from MI - 16.5 (6-24) for nonfatal CAD	- all deaths from AMI occurred in HLS treated with 42-45 Gy - all nonfatal CAD occurred in HLS treated with 44-45 Gy	No CAD disease or death from AMI occurred after RT with ≤ 30Gy, however the FU of these HLS was < 10 years.
+/-18 Age at MI 11-44yr	- < 5Gy: HR 0.7 (0.4-1.4) - 5-14Gy: HR 0.6 (0.1-2.5) - 15-34Gy: HR 2.4 (1.2-4.9) - ≥ 35Gy: HR 3.6 (1.9-6.9)	Childhood cancer survivors (13% HLS). End points assessed by questionnaires filled in by patients. HR compared to no cardiac RT group.

different treatment regimens in HL patients. All available large cohort studies with a sufficiently long follow-up period to detect CAD describe HLS who were treated during different periods with different treatments: chemotherapy, combined with RT of chemotherapy alone or RT alone. The doses RT are variable, as are the chemotherapy regimens. The few studies that compare the occurrence of CAD in HLS treated with different regimes were not designed to detect a difference between these groups. For example Aleman et al found that the risk for MI in HLS who were only treated with chemotherapy was not increased in comparison to the general population: Observed/Expected (O/E) MI = 1 (95% CI 0.1-3.5). However the subgroup of patients treated with chemotherapy only was small (n =71) in comparison to the HLS treated with RT only (n=406) and RT combined with chemotherapy (n=994).[8] The addition of chemotherapy to RT did not increase the risk for MI: O/E for RT only= 3.9 (2.7-5.4) vs. 3.9 (2.9-5.1) for RT + chemotherapy without anthracyclines and 3.5 (1.5-5.9) for RT + chemotherapy containing anthracyclines.[8] Similar results are described by Myrehaug et al who found the highest risk for cardiac hospitalization in the group treated with mediastinal RT and doxorubicin (HR=2.8, p<0.0001), the risk of the patients treated with RT only was slightly lower (HR=1.8, p=0.038) but the difference was not statistically significant (p=0.24). When looking at the hospitalization rates for MI/ischemic heart disease specifically, the O/E ratios were similar in the RT + doxorubicin group vs. RT only group: 2.4 (95% CI 0.8-7.2) vs. 2.8 (95% CI 0.9-8.4).[9]

3. When to start screening?

In contrast to radiation-induced valvular disorders which rarely occur within 10 years after RT, CAD has been diagnosed even within one year after RT.[13, 15, 51] This early CAD is thought to be caused by accelerated vascular damage in patients who already suffer from atherosclerosis and have other RF for CAD. This is best illustrated by the fact that in the young HLS population described by Hancock et al, with a maximum age at diagnosis of 21 years, the first AMI occurred 6 years after RT.[48] In an older population, Swerdlow found that 53/166 (32%) deaths from AMI occurred within 5 years after treatment.[13] Sixty-four percent of the AMI deaths occurred in patients older than 45 years at treatment. The prevalence of patients with previously diagnosed CAD or their risk profile was unfortunately not registered. Other studies have shown that

HLS with CAD within 5 years of RT have at least 2 traditional RF.[25, 34, 38] The median FU period between RT and symptomatic CAD is 9-13 years in most large cohort studies.[8, 15, 17, 25, 48] Aleman et al found a larger median interval of 19.5 years until the occurrence of MI.[8] In case series describing symptomatic CAD, the median FU time ranges from 14-28 years. [31, 34, 37, 38] In comparison to the general population, the risk for MI significantly began to rise 10 years after RT.

The question remains when premature arteriosclerotic disease after mediastinal irradiation starts to develop and when screening for asymptomatic disease should begin. There are scarce data about when asymptomatic CAD begins to develop.[18, 19, 26] In the cohort of 972 HLS who received >35 Gy to the mediastinum 53/345 deaths were attributed to heart disease (5.5% overall). Nine of the 33 deaths from acute myocardial infarction (27%) occurred before 40 years of age; 14 (42%) occurred within 10 years of treatment for Hodgkin lymphoma.[2] Based on these data and on the description of patients with asymptomatic CAD identified by screening, Heidenreich et al recommend to start screening for CAD 5 years after RT. Küpeli et al show a significantly different FU time from RT in HLS with coronary artery abnormalities (n=19) in comparison with HLS with normal CT-angiography(n=100): 14 years vs. 10 years p=.04.[19] The shortest FU from remission until detection of CAD was 5 years in a boy of 15 years without RF. Also other 37% (7/19) HLS with abnormal CT-angiography had a FU screening shorter than 10 years. The two patients with significant CAD needing revascularisation had a FU of 8 and 20 years.[19]

There is no minimal age limit for the development of CAD, even a boy of 12 years has been described who died of CAD seven years after RT, in the absence of traditional RF.[20]

These data suggest that screening for CAD should start five years after mediastinal RT in older HLS (≥45years) and 10 years after RT in younger HLS without traditional RF. In patients with coexisting RF, screening should be considered at an earlier stage, especially in the presence of ambiguous AP symptoms. There are no prospective studies that address the question whether or not patients with pre-existent CAD should be treated with mediastinal RT or with chemotherapy only. Myrehaug et al have shown that in HLS with pre-existent heart disease

are at increased risk for cardiac hospitalization when treated by mediastinal RT with or without chemotherapy HR 2.51 (1.06-5.94) and 2.70 (1.14-6.25) respectively when compared to HLS treated with chemotherapy only.[52] Many patients with possible concomitant atherosclerosis are treated with mediastinal RT, when considering that about 40% of HL is diagnosed in patients ≥45 years[53]. Future studies should investigate the best treatment regimen in these patients taking into consideration the increased risk for RT-induced CAD.

4. Which screening methods should be used?

Screening for CAD is not easy as the golden standard to detect obstructive CAD is CAG. This invasive method can not be performed in all HLS as the expected diagnostic yield probably does not outweigh the risks of this procedure. Therefore a non-invasive diagnostic procedure is needed to detect HLS at risk of CAD.

Alternative tests, as stress-induced ischemia detection by echography, ECG and scintigraphy, have been investigated. Many of these studies did not use CAG to evaluate the abnormalities identified with these non-invasive studies. Therefore test characteristics are difficult to compare with the golden standard.[54-56]

The largest study investigating non-invasive techniques in comparison to CAG demonstrated disappointing test characteristics of the non-invasive tests.[2] In this study, 294 HLS were screened for CAD by ECG, echocardiography and radionuclide perfusion imaging at one stress session. CAG was subsequently performed in 40 patients with abnormal results at stress imaging, at the discretion of the physician. Twenty-two patients showed ≥50% stenosis, 11 had stenosis < 50% and seven had a normal CAG. Within the 40 patients who underwent a CAG, sensitivity and specificity to detect stenosis ≥50% were 59% and 89% for stress echocardiography, 65% and 11% for nuclear scintigraphy and 38% and 100% for stress ECG. Of 20 patients with ST depressions >1mm on stress ECG, 12 did not undergo CAG because they were asymptomatic and showed no abnormalities on stress imaging. Test characteristics of the stress ECG can only been interpreted in patients with abnormal stress imaging. The combination of three tests revealed seven false positive results for any CAD. This approach only identifies patients with a positive stress test; the amount of false negative results can not be calculated. At least some patients with CAD were not

detected by this screening approach, as during a median follow-up of 6.5 years, 23 patients developed symptomatic CAD (including 10 AMI, of which two fatal). Of these, six events occurred within 2 years after screening. No details were provided on the results of the screening tests of these patients.

The value of non-invasive testing in diagnosing CAD was correlated to CAG in two smaller studies.[18, 26] By screening asymptomatic patients by stress ECG, and myocardial scintigraphy, Gustavsson et al identified 1 out of 24 patient with CAD. Because this low incidence, no test characteristics can be calculated for the different tests (CAG was only performed in this patient).[18] Glanzmann et al describe findings of exercise ECG and myocardial scintigraphy using 99mTc-MIBI in 144 HLS.[26] They detected 4 out of 144 (2.8%) patients with CAG-confirmed CAD who had typical ischemia signs on the scintigraphy and exercise ECG. One other patient had unequivocal signs of ischemia only on stress ECG. Of five patients with CAD detected by screening, two underwent revascularization. Routine CAG was not performed in all patients; calculation of false negative results of stress ECG and scintigraphy were, therefore, not possible. Two patients with normal screening tests and without AP had a fatal MI less than six months after testing. A third patient with a non-fatal MI reported increased fatigability but had normal tests, four months before the MI.

These results stress the need for more accurate, non-invasive screening tests for CAD. New diagnostic tools, like CT-, MRI-angiography and coronary artery calcium (CAC) score measurements, have been developed. Computed tomography can noninvasively detect and quantify CAC using serial thin section (3 mm) tomograms from the aorta through the apex of the heart. The sensitivity and specificity for the presence of significant (≥50%) angiographic stenosis vary with the amount of CAC. Diagnostic accuracy can be improved by the use of age- and gender-specific threshold values. As the CAC score varied from >20th percentile to >75th percentile for age, the sensitivity fell from 97-81% in men and from 98-76% in women but the specificity increased up to 77% in predicting significant stenosis. As to the predictive value of CAC score for clinical end-points in the general population, asymptomatic subjects with a CAC of zero had no cardiac event after a FU of mean 40 months.[57] Furthermore, a CAC score above the 75th percentile had

a positive predictive value of 45% for MI or cardiac death within 40 months.[57]

Three studies have used these diagnostic tools in HLS.[10, 19, 31] Andersen et al performed CAC score measurements in 47 HLS treated with mediastinal RT, mean age 50 years. Seven patients already had verified CAD and had high CAC.[10] Of the remaining 40 HLS, eight had a CAC of zero. Twenty-seven had a CAC between 1 and 199 and five had a CAC score between 200 and 999. Probably many of the HLS described by Andersen had a CAC score above the 75th percentile adjusted for the age and gender (for example the 75th percentile for a male and a female of 59 years is 201 and 25 respectively).[58] Unfortunately there are no follow-up data available of this cohort and no CAG was performed to asses the severity of CAD.
In a pilot study Rademaker et al present the results of CAC score en CT-angiography in nine HLS. Eight patients had a CAC score above the 75ste percentile adjusted for age and gender.[31] One patient had a CAC score of zero. All eight HLS with a high CAC score, had CAD on CT-angiography: three had stenoses < 50%, two patients died soon after the investigations and did not undergo further evaluation and three patients underwent further investigations (one underwent an angioplasty, one a two vessel CABG and one a normal stress echocardiogram and underwent risk profile modification). No follow-up data are presented. This study shows the potential of screening asymptomatic HLS by CAC scores and CT-angiography, but also the need for performing additional stress tests to confirm significant CAD.
In another recent study, Küpeli investigated 119 HLS by CT-angiography and found coronary artery abnormalities in 19 (16%).[19] Based on these findings, four were eligible for a CAG. One patient with ≥70% stenosis in the proximal LAD refused CAG. Stent implantation was performed in a second patient because of 90% osteal stenosis in the RCA. The remaining two patients showed only some wall irregularities on CAG and were taken to close medical follow-up, as were the remaining 15 patients.
More studies should be performed in which different combinations of non-invasive screening tests are performed in HLS. Clinical evaluation, stress-ECG and stress-scintigraphy have shown poor diagnostic

properties in detecting CAD in asymptomatic HLS. Recent data on CAC measurements and CT-angiography show more promising results, while their prognostic yield still has to be determined in HLS in relation to the possible disadvantages as radiation burden (one CAC measurement is equivalent to 30 chest x-rays) and cost aspects (cost effectiveness was difficult to assess in the studies performed so far with CAC measurements).[59] The 2007 American College of Cardiology/American Heart Association (ACC/AHA) guideline on CAC scoring recommended the use of CAC scores in populations at intermediate ten year risk (between 10 and 20%) of CAD.[59] The ten year risk of CAD in HLS subgroups is difficult to estimate considering that there are many unknown factors, but cohort studies found an incidence of CAD between 1-16% (Table 2), which categorizes HLS in the low-intermediate risk group for CAD. Considering these findings, it can carefully be recommended that serial determination of CAC score would be beneficial in HLS. HLS who have a low-risk of CAD based on a CAC-score of 0 and a low NCEP/ATP III score can be followed-up at 5 years intervals as the 5-year mortality is <1% in the general population.[60] However, a CAC score of 0 will not completely rule out CAD as non-calcified plaques can still be present, therefore HLS should still be encouraged to avoid traditional RF for CAD and to be alert for signs and symptoms of CAD. Patients with higher CAC score, especially those with a score above the 75th percentile should undergo further screening either by CT-angiography and/or stress tests, or medical therapy should be started aimed at lowering the cholesterol levels and lowering the blood pressure to levels appropriate for patients in the highest risk categories for CAD (Figure).

Valvular disorders

HLS are also at increased risk of developing valvular disease. In two large retrospective cohort studies, the incidence of valvular disorders was 6% and 11% after a median of 22 (range, 6-31) and 23 (range, 5-37.8) years respectively. [8, 17] Information about the relevance of the diagnosed valvular disease was not given. The incidence of clinically relevant valvular disease varies in several cross-sectional screening studies.[18, 20, 21, 56, 61-64] This is most probably due to the differences in patient numbers, follow-up time and treatment modalities (Table 3). The definition of clinically relevant valvular disease is a matter of de-

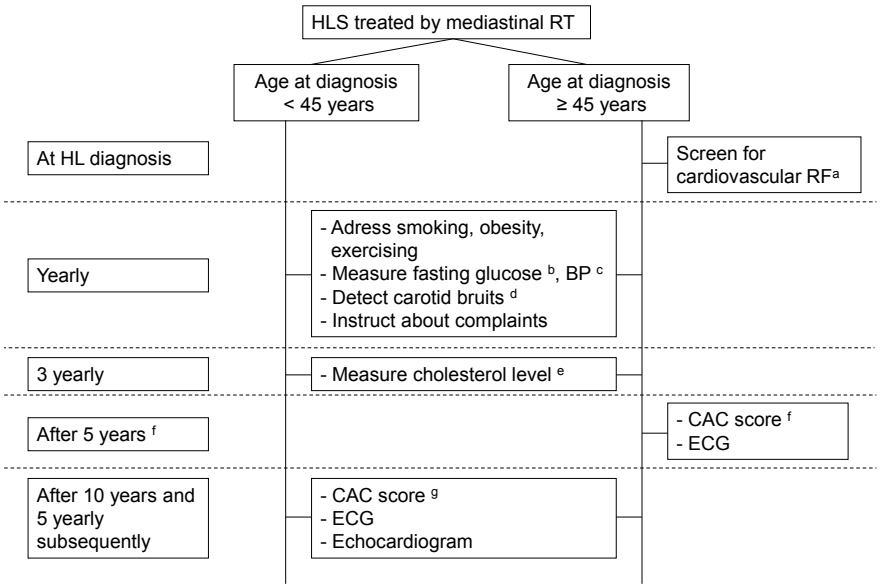

Figure 1 Cardiovascular screening program in HLS.
BP blood pressure; CAC coronary artery calcium; ECG electrocardiogram; HLS Hodgkin lymphoma survivors; RF risk factor; RT radiotherapy.

[a] Cardiovascular RF: hypercholesterolemia, hypertension, obesity, smoking, positive family history of cardiovascular disorders, history of cardiovascular disorders. In case of previous cardiovascular disease or a high risk profile (including cardiovascular complaints), consider treating HL without RT to the mediastinum.
[b] Treat diabetes mellitus according to the ADA/EASD guidelines[44], considering RT as one risk factor for atherosclerosis.
[c] Treat hypertension according to the JNC 7 guidelines[45], considering RT as one risk factor for atherosclerosis.
[d] In HLS treated by cervical RT.
[e] Treat hypercholesterolemia according to the NCEP ATP III guidelines[46], considering RT as a risk factor.
[f] Also perform measurements of CAC score after 5 years in HLS <45 years at diagnosis with ≥ 2 RF for cardiovascular disease.
[g] In case of a CAC-score >0 referral to a cardiologist for ischemia detection. If no ischemia is detected on additional testing and there are no cardiac symptoms, repeat CAC-score in 5 years. In case of an augmentation of the CAC-score during subsequent testing, ischemia detection should be repeated as well.

bate. In older studies, relevant valvular disorders were defined as the need for endocarditis prophylaxis.[26, 61] Since the 2008 update of the ACC/AHA guideline, endocarditis prophylaxis is no longer indicated in patients with acquired valvular disorders without prosthetic valves.[65] The rationale of screening asymptomatic HLS for valvular disorders will be discussed in the next paragraph.

Why screening asymptomatic patients?

The rationale of identifying asymptomatic valvular disorders in HLS is to find individuals who can benefit from conservative medical treatment and close monitoring. [66] It is a matter of debate whether asymptomatic HLS with severe valvular disorders could be eligible for early valvular surgery.

According to ACC/AHA guidelines, valvular surgery is indicated in some asymptomatic patients with significant valvular disorders in case of left ventricular (LV) dysfunction.[66] However, caution is recommended when considering valve replacement in asymptomatic patients with radiation-induced valvular disease. There is no evidence based consensus on indication and timing of valvular replacement in RT-induced valvular disease. The ACC/AHA guideline suggests surgery only in patients with significant symptoms or concomitant CAD. This recommendation points towards the increased surgical risks in radiation-induced valvular disease, mainly caused by pericardial and pulmonary fibrosis. The peri-operative mortality of about 13% in HLS undergoing valvular surgery is significantly higher than in patients treated with less extensive mediastinal irradiation (breast cancer, lung cancer, non-Hodgkin lymphoma etc.): 4%.[67, 68] However, these authors advocate early surgical intervention to avoid the development of risk factors like severe symptoms, LV dysfunction, cardiac failure or atrial fibrillation (AF). These are associated with a worse long term outcome.[68] One may argue that the increased mortality in these patients was caused by late presentation and advanced disease. Furthermore, high peri-operative mortality rates are observed in patients with present or previous restrictive pericarditis: 4/10 (40%) comparing to those without pericarditis 3/50 (6%).[68] As restrictive pericarditis is less often encountered since modern radiation modalities are used, one can expect that the high surgical mortality associated with this comorbidity will decrease in the future. Furthermore, less invasive procedures like endovascular valvular replacement have not yet been evaluated in HLS.Up till now there have been no RCT's comparing the outcomes of valvular surgery in symptomatic vs. asymptomatic patients with radiation-induced valvular dysfunction. The incidence of valvular surgery in HLS is low and varies from 0.5% (3/635) to 2.4% (10/415) and 5.8% (3/51) in 3 studies. The difference in incidence can in part be explained by different FU periods

Table 3 Screening studies describing valvular disease in HLS. ABVD adriamycin, bleomycin, MVP mitral valve prolapse; PV pulmonal valve; RT radiotherapy; SD standard deviation;

Study	Nr. of HLS	Median age at treatment (SD/range)	Median FU in years (SD/range)	Treatment type	AV regurgitation
Pohjola [20] 1987	28	32 (12-38)	9 (5-14)	All mediastinal RT mean 38Gy (34-47Gy). No CT.	4%
Gustavsson [18] 1990	25	38 (21-45)	15 (4-20)	All mantle field RT mean 40Gy (35-43Gy). No CT.	4%
Kreuser [21] 1993	49	35 (15-58)	5 (2-10)	All CT (COPP/ABVD), mantle field RT in 63%.	moderate 2%
Glanzman [26] 1994	112	31 (10-58)	10 (1-27)	All RT. Doses between 30-45 Gy. CT in unknown number of patients.	- mild: 2.7% - moderate: 0.9% - mild AV regurgitation and AV stenosis: 2.7%
Lund [64] 1996	116	Age at HL<50 Age at FU:37	9 (3)	All mediastinal RT mean 40.6 ± 1.4Gy. 66% CT.	17%
Heidenreich [61] 2003	294	42 (9)	15 (7)	All mantle field RT mean 43± 0.3Gy. 56% CT.	mild: 21% - 3.4% after 2-10yr ‡ - 20% after 11-20yr - 45% after >20yr moderate/ severe: 5.1% - 1.1% after 2-10yr - 2.3% after 11-20yr - 15% after >20yr
Adams [56] 2004	47	16.5 (6-25)	14 (6-25)	All RT mean 40Gy (27-51Gy). CT in 4 patients.	≥ mild: 19%
Greenfield [63] 2006	58	23 (7-34)	17 (4-36)	All mantle field RT mean 35Gy (27-39 Gy). 72% CT	≥mild 9%

[a] On right sided cardiac catheterization a mild PV stenosis was found in 7% and 4% had a subvalvular stenosis over the PV.
[b] All patients with AV stenosis also had mild AV regurgitation.
[c] All grade >1 (none of the 40 control subjects had these abnormalities)
[d] MV stenosis in 2%
[e] Mixed aortic valve abnormality (stenosis or ≥ mild regurgitation): 9%
‡ FU from RT
* not statistically different from expected.

and vinblastine, dacarbazine; AV aortic valve; CT chemotherapy; FU follow-up; MV mitral valve; TV tricuspidal valve.

MV regurgitation	TV regurgitation	PV regurgitation	AV stenosis	Other
-	-	-	4%	[a]
mild: 32% moderate 4%	mild: 84% moderate: 4%	35%	-	
-	mild 7.3%	-	-	
- in patients with MVP: - mild MR: 4.5% - moderate MR: 0.9% - in patients with mitral sclerosis : 2.7%	6.3%	-	mild: 1.8% rate: 0.9%	[b]
10%	5%	2%	-	[c]
mild: 36% - 24 % after 2-10yr - 37% after 11-20yr - 48% after >20yr moderate/ severe: 3.4% - 2.3% after 2-10yr - 3.8% after 11-20yr - 4.1% after >20yr	mild: 15% - 9% after 2-10yr - 14% after 11-20yr - 22% after >20yr moderate/ severe:1.4% - 0% after 2-10yr - 0.8% after 11-20yr - 4.1% after >20yr	mild: 7% - 2 % after 2-10yr - 7% after 11-20yr - 12% after >20yr moderate/ severe:0%	4% - 2-10 yr: 0% - 11-20yr: 1% - >20yr: 16%	
≥ mild: 21%	≥ mild: 26%*	any grade 2.6%	6%	[d]
≥ mild: 5,2%			9%	[e]

of the cohorts of 10, 11 and 22 years respectively.[17, 48, 69] The incidence of valvular replacement will rise as these cohorts will be followed for a longer period; the median FU from RT until diagnosis of moderate or severe valvular disorder was 22 years in a large cohort (n=415).[17]

Timing of valvular surgery is often influenced by the need for other cardiac interventions; many patients undergo combined surgery. A single or multiple valvular procedure was often combined with CABG, aortic surgery or pericardectomy.[67, 68] Authors state that they combine revascularization surgery with valvular interventions to avoid a second intervention which may be difficult due to fibrosis after RT. Establishing timing and indication of surgery is complex and should be individualized based on complaints and expected outcome. As CAD has been shown to develop earlier than valvular disorders after mediastinal RT,[8] it is important to thoroughly investigate the valves and consider a concomitant valvular intervention in patients undergoing CABG.[39] A long ischemic time during surgery is associated with a poor post-operative prognosis. So the risk of prolonging the operation time to perform a valvular intervention, should be weighted against the difficulty of performing a second operation after some years for the valvular disorder.[68]

There are no studies in HLS investigating the benefit of close follow-up by a cardiologist and of medical treatment on delaying symptoms from valvular disorders or improving outcome. A high percentage of HLS have been shown to have chronic valvular disorders. [69] The ACC/AHA guideline recommends specific medical interventions by cardiologists in these patients.[66] Close follow-up by a cardiologist is particularly warranted in asymptomatic patients with severe aortic stenosis (AS); these patients are at increased risk of sudden death, before symptoms occur. This risk can be reduced to less then 1% per year when these patients are closely followed prospectively.[66] Patients with aortic regurgitation (AR) can remain asymptomatic until severe LV dysfunction has developed. LV systolic function is the most important determinant of postoperative survival, thus patients should be monitored carefully and surgery should be performed timely.[66] In patients with more than a mild degree of mitral stenosis (MS), counseling on avoidance of severe physical stress is advised. Patients with MS are prone to develop AF, increasing the risk of stroke. Patients with mitral regurgitation (MR) are also at increased risk of developing AF. In patients with functional

or ischemic MR and LV systolic dysfunction, primary treatment of the LV systolic dysfunction with ACE inhibitors or beta blockers and biventricular pacing have all been shown to be beneficial.[66]

Following asymptomatic valvular disorders in time will help establishing whether the valvular disorder is responsible for emerging dyspnea. If this is the case, making a decision on whether a valvular intervention is needed will be easier. Dyspnea (on exertion) can be caused by a number of other causes besides valvular disorders in HLS.[20, 70] Lund et al investigated the cardiac and pulmonary sequelae in a group of 116 long-term survivors of HL.[70] They classified the patients according to the diagnosis of a cardiac, pulmonary or combined abnormality. They found that dyspnea on exertion was a complaint present in all subgroups of abnormalities: combined cardiopulmonary 59%, pulmonary only 38%, cardiac only 12% and also in patients with no detected sequelae 22%.

2. Whom to screen?

In a large cohort study of childhood cancer survivors, radiation doses between 15-34Gy and ≥35Gy were associated with a significant HR of 3.3 an 5.5 respectively, when compared to patients treated without mediastinal RT.[49] Patients who were only treated with chemotherapy have been shown to have the same risk for developing valvular disorders as the general population.[8] However patients treated with RT and anthracyclines had a twofold increased risk of valvular disorders, on top of the effect of mediastinal RT, especially when the anthracycline dose was ≥250mg/m2.[8, 49] The role of patient related covariates remains questionable; Aleman et al found a significant higher risk for valvular disorders in HLS with hypercholesterolemia (HR 1.65) and diabetes mellitus (HR 1.81). This was not confirmed in the study by Hull et al.[17]

Some authors have suggested that female RT survivors have a higher risk of developing valvular disorders than men.[8, 49, 70, 71] In a large retrospective cohort of 1474 HLS, among 356 cardiac events in men, 19% consisted of valvular disorders, compared to the 36% valvular disorders from the total 263 cardiac events observed in women.[8] In a screening study, 41% of the women and 16% of the men had a valvular dysfunction, despite comparable base-line and treatment characteristics.[70] The authors could not find an explanation for this difference. Other studies

did not confirm this finding.[17] Young age at treatment was also shown to be associated with a higher risk for developing valvular disorders, especially in patients treated before the age of 10 years, compared to patients treated between 15-20 years of age.[49] However the cumulative incidence of valvular disorders at 30 years of FU was only 4% in childhood cancer survivors (age less than 20 years at treatment) [49] compared to 20% in an older population of HLS treated before 41 years of age.[8] The 4% cumulative incidence found in the total group of childhood cancer survivors will be higher in the subgroup of HLS, as HLS had the highest HR of developing valvular disorders of 10.5, compared to 4.8 for the whole group.[49]
Considering the inconsistent findings from the different studies we recommend screening all HLS for valvular disorders, until more data will become available confirming the different risk factors suggested above.

3. When to begin screening?

Screening should begin when patients start developing valvular disorders for which close monitoring, medical treatment or valvular replacement surgery is needed. These end-points have not been identified as such in HLS. As shown in Table 3, screening studies only report the incidence of valvular abnormalities without uniformly stating their importance or consequence. Heidenreich et al found that moderate or severe valvular abnormalities were present in 42/294 (14%) of HLS. Of these, only 3/294 (1%) presented with symptoms within 10 years of follow-up. Another 10 and 29 patients presented after a FU of 11- 20 years and ≥20 years respectively. There are no prospective data about the course of their disorders.
There is only one prospective study which re-evaluated the valvular disorders at a median of 12 years after the first screening echography.[69] In the first article, 116 HL survivors were studied by echocardiography in 1993.[64] At that time they had a median follow-up of 10 years and moderate AR and MR were present in 36 (31%). One patient was identified with a severe valvular dysfunction (MR) for which he received a prosthetic valve. In 2005, 51 patients were re-evaluated at a median follow-up of 22 years after RT.[69] Of the 14 patients with no AR or MR in 1993, 13 (93%) had developed a new abnormality, none of these was severe. Of the 37 patients with an identified abnormality in 1993, 12

(32%) had an unchanged status of the MR or AR. Twenty-five patients (68%) had either worsened MR, AR or developed a new abnormality. Of these 25, two had received a valvular operation (including the patient with a severe MR at the first screening) and four progressed to severe MR or AR. Of the whole investigated group in 2005, 20/51 (39%) had a new AS, an anomaly that was not present in any HLS in 1993. One patient with a normal echocardiography in 1993 developed a severe AS before 2005 for which he needed an AV replacement.

The rate of occurrence of valvular disorders in these studies justifies starting screening for valvular disorders 10 years after mediastinal RT. However, this suggestion applies to patients who were treated with higher RT doses than are used nowadays and who have mostly already exceeded a 10 year latency period from RT. Thus we recommend performing a first screening echography to detect valvular disorders in all patients treated with mediastinal RT at a dose of more than 35Gy or with older RT techniques.

There is no data available yet on adult patients who have been treated with less extensive and lower dose mediastinal RT. Aleman et al found however that HLS treated with mediastinal RT and anthracyclines seem to develop valvular disease earlier than HLS who were treated with RT alone, after 14 respectively 18 years of FU.[8] Combined modality treatment with anthracycline chemotherapy and lower dose RT is the standard therapy nowadays in stage I and II HL. The dose RT has been lowered but the addition of anthracyclines may increase the risk of developing valvular disorders which may also occur earlier. Therefore we also recommend a first echocardiography after 10 years of FU in HLS treated with modern combined modality therapy. In case no valvular disorders are detected, the next screening echocardiography should be performed every 5 years subsequently. A close cardiologic follow-up according to the ACC/AHA guidelines should be performed in case valvular disorders are found.

4. Which screening methods should be used?

All valvular abnormalities have been detected by echocardiography in previously published studies. Heart auscultation for murmurs can also be a good screening method to detect valvular dysfunction when assessed by an experienced physician. The diagnostic yield of heart auscultation by an attending radiation or medical oncologist blinded

to the outcome of the echocardiography was prospectively assessed in one study.[61] The physical examination in these asymptomatic HLS following mediastinal RT proved to be little informative, with a positive predictive value of 25% for a systolic murmur to detect aortic stenosis, moderate mitral or tricuspid regurgitation. The sensitivity for a diastolic murmur to detect mild or greater aortic regurgitation was 5%. For this reason we recommend that all HLS treated with mediastinal RT should undergo a first screening for valvular disease by transthoracic echocardiography.

Pericardial disease

The most prevalent and frequently described cardiac complication of mediastinal RT used to be pericarditis.[48, 72] Patients with constrictive pericarditis had typical complaints of fatigue, peripheral edema, breathlessness, and abdominal swelling.[73] Nowadays it rarely occurs since the LV has been shielded, thereby diminishing the total radiation dose on the heart. In a recent study, asymptomatic HLS treated with RT and a LV block were screened for pericarditis.[61] Although 21% (62/294) had a thickened pericardium and small pericardial effusions were present in 3%, no patients had wall-motion abnormalities or Doppler findings suggestive of constrictive pericarditis. The course of occult pericarditis identified by screening has been shown to be mild. Of the 13 patients with occult pericarditis identified by Applefeld et al, none had to undergo pericardectomy, as their symptoms were not incapacitating.[72]

The prognosis of patients who develop symptomatic radiation-induced constrictive pericarditis is poor.[68, 72, 74] Karram et al identified six patients with radiation-induced pericarditis and found that all had deceased at a median of 10 months after the diagnosis of pericarditis.[75] In a surgical series, a 5-year survival after pericardectomy for RT-related cases was only 51% compared with 83% for non-RT-related cases.[76] The poor outcome with RT-induced constriction is probably multi-factorial and is to be expected in patients with other co-morbidities like pulmonary fibrosis or myocardial, valvular or coronary damage.[75] A comprehensive evaluation should thus take place before pericardectomy is performed.

Because of the diminished prevalence and mild course of occult pericarditis, we do not recommend routinely screening asymptomatic HLS

for constrictive pericarditis. HLS should undergo serial echocardiography, also as part of screening for occult valvular disorders. The presence of a thickened pericardium, pericardial effusion and other Doppler parameters characteristic for constrictive pericarditis should be recorded and followed in time. However, the diagnosis of pericardial disease can often be challenging, as it is not always accompanied by thickened pericardium.[77]

Cardiomyopathy

RT-induced myocardial fibrosis has been demonstrated in pathological studies and is thought to be caused by microvascular injury.[78, 79] The predominant clinical picture related to these changes is restrictive cardiomyopathy characterized by diastolic dysfunction. Systolic dysfunction is more common in those who also received an anthracycline and high radiation dose.[55, 61] In contrast to systolic dysfunction which has decreased in frequency, diastolic disorders are still encountered in HLS. The prevalence of diastolic dysfunction was comparable in two studies using modern RT techniques.[55, 80] Heidenreich et al found mild and moderate diastolic dysfunction in 9% and 5% of 294 investigated HLS.[80] Patients with diastolic dysfunction were older, more likely to have hypertension or diabetes, had received higher dose RT and had a long latency period from RT. CAD related events were more common in patients with diastolic dysfunction 4/40 (10%) than in patients with normal diastolic function 5/242 (2%, p=0.005). The authors hypothesize that CAD can be another cause of diastolic dysfunction.

As there is no evidence that medical therapy can alter the course of asymptomatic diastolic dysfunction, routine screening has not been recommended in asymptomatic HLS to detect myocardial damage. In patients presenting with signs of congestive heart failure (CHF), first other, more common and treatable causes of CHF (such as silent ischemic, hypertensive or valvular heart disease) should be excluded.[81] Diastolic and systolic function measurements should be part of the routine cardiac screening program. Special attention should be paid to women who want to become pregnant after therapy for HL, as occult cardiomyopathy can become symptomatic during pregnancy.[82]

Arrhytmias and conduction system disease

Conduction abnormalities have been associated with mediastinal RT, especially as very late effects and in patients who did not receive sub-carinal blocking.[61] There are two types of injury: a direct damage to the cardiac conduction system and dysfunction of the autonomic regulatory system. RT can result in fibrosis of tissue adjacent to the conduction system resulting in a wide spectrum of abnormalities like QT-interval prolongation, sick sinus syndrome, all forms of atrioventricular (AV) block, and bundle branch block. The incidence of these defects varies widely. Some demonstrate no ECG abnormalities,[21, 83] others with similar cohort sizes and follow-up report ECG abnormalities in 46 and 48% of HLS.[20, 22] In patients with AV block, the level of the block is usually infranodal and the progress to third-degree AV block occurs 10-20 years after RT.[84] In patients with bundle branch block, right bundle abnormalities tend to be more common.[20, 24, 61, 62] The true incidence of severe symptomatic conduction anomalies is not known since this has only sporadically been reported. Most symptomatic presentations involve complete heart block and syncope.[81]

All these are easily identifiable by a routine ECG. We recommend performing an ECG at every cardiac evaluation moment, especially as conduction system disease tends to occur in HLS who have other forms of radiation induced heart disease.

Carotid disease and other vascular abnormalities

Atherosclerosis of the carotid arteries is a well-known late treatment effect of RT [85, 86], but has only scarcely been described in sites other than the coronary arteries in HLS. The only study in which 42 asymptomatic HLS are screened by modern Duplex ultrasonography of the carotid arteries identified 24% of patients with intima-media abnormalities that did not cause significant stenosis.[87] Only one patient had ≥70% stenosis of both common carotid arteries. In this young group of HLS (mean age 27 years at HL diagnosis) followed for a mean of 13 years after treatment the intima-media thickness was significantly higher in irradiated patients compared to non-irradiated patients and to age-matched control subjects. A longitudinal study is needed to asses the importance of these minor changes. The low prevalence of significant carotid artery stenosis can be explained by the young age of the cohort and the short follow-up. In a large cohort study by Hull et al

(n=415), non-coronary atherosclerosis in young HLS (median 20 years at diagnosis of HL) has been shown to have a long latency of median 21 years.[17] This subgroup of patients had lesions not commonly seen in the general population, like isolated carotid or subclavian artery stenosis ≥40%. These lesions are thought to be caused by endothelial cell loss which in turn can cause progressive atherosclerosis many years later.[17] When examining the patients who experienced transient ischemic attack (TIA) or stroke, the median age when they underwent RT was 51 years and the median FU from therapy to event was only 5.6 years. The authors believe that the difference between these two subgroups lies in the fact that the older subgroup probably had pre-existent atherosclerosis which was accelerated by RT. In total 7.4% of HLS had developed carotid and/or subclavian artery disease at a median of 17 years after treatment.[17]

A recent multicenter cohort study in 2201 HLS treated before age 55 confirms a twofold and threefold increased risk of stroke and TIA in HLS, when compared to the general population.[88] The median time interval from RT until stroke diagnosis was 17.4 years (the authors only included HLS who survived 5 year after therapy). The cumulative incidence of ischemic stroke or TIA 30 years after HL treatment was 7%. The excess burden was one excess case each of stroke and TIA among hundred HLS followed for 10 years. The most important RF associated with cerebrovascular events was RT to the neck. Modifiable RF like hypertension, hypercholesterolemia and diabetes mellitus were also associated with the occurrence of stroke or TIA. The risk for ischemic stroke or TIA was twofold higher in HLS with cardiac disease than those without the cardiac disease. This can be explained by the fact that besides atherosclerosis of the carotid arteries, cardio-embolisation can also cause stroke and TIA's. The etiology of the cerebrovascular event could be established in 80% of cases and was due to large vessel atherosclerosis in 43% and 28% of patients with ischemic strokes and TIA respectively. A cardioembolic source was identified in 18% and 31% of patients with ischemic stroke and TIA. Results of carotid Duplex imaging could be retrieved in 66% of patients and showed substantial (≥50%) carotid stenosis in 20% of patients who suffered from ischemic stroke and 13% of patients who experienced a TIA. Furthermore 41% had no stenosis at all.[88]

The authors do not advocate screening in asymptomatic patients because of the relatively low excess cases of stroke and TIA. Moreover, the management of asymptomatic patients with more severe carotid arterial disease will provide clinicians with a management dilemma in which the risks of progression and stroke have to be weighted against the risks of surgical or percutaneous interventions. The best treatment for asymptomatic carotid artery stenosis is a matter of debate and should be patient tailored.[87, 88] Treatment of the traditional RF is very important, as they are associated with cerebrovascular disease.
Screening for carotid stenosis should be considered in patients who have symptoms of vascular damage at other sites.[16] Patel et al present 21 patients with RT-induced noncoronary atherosclerotic vascular disease and found that eight patients had atherosclerosis at more than one site.[16] They also emphasize the importance of recognizing less specific symptoms at an early stage. Carotid artery involvement was fatal or resulted in permanent hemiparesis when stroke was the presenting symptom. All patients presenting with amaurosis fugax, visual field distortion or a carotid bruit however have not developed adverse neurologic sequelae because they could be treated on time. Other presentations of noncoronary vascular disease were postprandial pain as a sign of intestinal angina as result of stenosis of the superior mesenteric artery. A difference in blood pressure between arms, breast and axillary edema, or a subclavian bruit were signs of subclavian artery stenosis. When the arteries to the legs are exposed to radiation patients may develop atherosclerosis leading to intermittent claudication.

Based on these data we agree with De Bruin et al that routine screening of asymptomatic HLS for carotid artery disease is not advisable. However, future prospective studies should be performed in which HLS are identified which have an increased risk of stroke. The yield of yearly screening HLS for carotid bruits is unknown and should also be addressed in future studies. Furthermore, atrial fibrillation should be treated as it contributes to the high risk of stroke and TIA. Physicians should pay special attention to symptoms of non-coronary artery disease at sites at which HLS have been irradiated. HLS complaining from such symptoms should be referred timely to a neurologist or vascular specialist.

Conclusion

There are only few studies investigating the importance of screening asymptomatic HLS for cardiovascular disease. Furthermore these studies describe HLS treated with strategies that are mostly not in use any more, making it difficult to compose screening programs for the patients treated currently. Screening these patients is important because they are at increased risk of developing disabling late cardiovascular sequelae which contribute to increased mortality at a relative young age. We suggest a cardiovascular screening program (Figure) starting five years after mediastinal RT in patients older than 45 years at diagnosis and in younger patients with ≥ two RF for cardiovascular disease. These patients are at increased risk of pre-existent atherosclerosis which can be accelerated by RT. HLS diagnosed at a younger age and who do not have cardiovascular RF should be screened starting 10 years after mediastinal RT. Subsequently, patients without signs or symptoms of CAD or valvular disease can be followed at 5 year intervals by CAC-score measurements and echocardiography. When these signs appear, prompt referral to a cardiologist is warranted for close follow-up and timely intervention. Moreover, patients should be instructed to contact their physician in case cardiovascular symptoms develop and their traditional cardiovascular RF should be addressed. We suggest determining a cardiovascular risk profile at diagnosis of HL in patients older than 45 years. In case of a high risk, treating HL without RT should be considered. Prospective studies are needed to confirm the value of these screening tests in HLS. Screening programs should also be evaluated with regard to the long-term impact on survival of HLS and their cost-effectiveness.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71-96
2. Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for hodgkin's disease. *J Clin Oncol*. 2007;25:43-49
3. Kleikamp G, Schnepper U, Korfer R. Coronary artery and aortic valve disease as a long-term sequel of mediastinal and thoracic irradiation. *Thorac Cardiovasc Surg*. 1997;45:27-31
4. Ng A, Constine LS, Advani R, et al. Acr appropriateness criteria: Follow-up of hodgkin's lymphoma. *Curr Probl Cancer*. 2010;34:211-227
5. National comprehensive cancer network: Nccn clinical practice guidelines in oncology: Hodgkin lymphoma, 2010. Http://www.Nccn.Org/professionals/physician_gls/f_guidelines.Asp.
6. Children's oncology group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, 2008. Http://www.Guidelines.Gov/summary/summary.Aspx?Ss=15&doc_id=10772&nbr=5600.
7. Mauch PM, Kalish LA, Marcus KC, et al. Long-term survival in hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am*. 1995;1:33-42
8. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for hodgkin lymphoma. *Blood*. 2007;109:1878-1886
9. Myrehaug S, Pintilie M, Tsang R, et al. Cardiac morbidity following modern treatment for hodgkin lymphoma: Supra-additive cardiotoxicity of doxorubicin and radiation therapy. *Leuk Lymphoma*. 2008;49:1486-1493
10. Andersen R, Wethal T, Gunther A, et al. Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of hodgkin's lymphoma. *Am J Cardiol*. 2010;105:149-152
11. Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for hodgkin's disease. *Cancer*. 1992;69:1241-1247
12. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of hodgkin's disease. *JAMA*. 1993;270:1949-1955
13. 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;99:206-214
14. Lee CK, Aeppli D, Nierengarten ME. The need for long-term surveillance for patients treated with curative radiotherapy for hodgkin's disease: University of minnesota experience. *Int J Radiat Oncol Biol Phys*. 2000;48:169-179

15. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, van Putten WL, Levendag PC. Ischemic heart disease after mantlefield irradiation for hodgkin's disease in long-term follow-up. *Radiother Oncol*. 1999;51:35-42
16. Patel DA, Kochanski J, Suen AW, et al. Clinical manifestations of noncoronary atherosclerotic vascular disease after moderate dose irradiation. *Cancer*. 2006;106:718-725
17. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama*. 2003;290:2831-2837
18. Gustavsson A, Eskilsson J, Landberg T, et al. Late cardiac effects after mantle radiotherapy in patients with hodgkin's disease. *Ann Oncol*. 1990;1:355-363
19. 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*. 2009
20. Pohjola-Sintonen S, Totterman KJ, Salmo M, Siltanen P. Late cardiac effects of mediastinal radiotherapy in patients with hodgkin's disease. *Cancer*. 1987;60:31-37
21. Kreuser ED, Voller H, Behles C, et al. Evaluation of late cardiotoxicity with pulsed doppler echocardiography in patients treated for hodgkin's disease. *Br J Haematol*. 1993;84:615-622
22. Gottdiener JS, Katin MJ, Borer JS, Bacharach SL, Green MV. Late cardiac effects of therapeutic mediastinal irradiation. Assessment by echocardiography and radionuclide angiography. *N Engl J Med*. 1983;308:569-572
23. Pihkala J, Happonen JM, Virtanen K, et al. Cardiopulmonary evaluation of exercise tolerance after chest irradiation and anticancer chemotherapy in children and adolescents. *Pediatrics*. 1995;95:722-726
24. Watchie J, Coleman CN, Raffin TA, et al. Minimal long-term cardiopulmonary dysfunction following treatment for hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1987;13:517-524
25. King V, Constine LS, Clark D, et al. Symptomatic coronary artery disease after mantle irradiation for hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1996;36:881-889
26. Glanzmann C, Kaufmann P, Jenni R, Hess OM, Huguenin P. Cardiac risk after mediastinal irradiation for hodgkin's disease. *Radiother Oncol*. 1998;46:51-62
27. Reber D, Birnbaum DE, Tollenaere P. Heart diseases following mediastinal irradiation: Surgical management. *Eur J Cardiothorac Surg*. 1995;9:202-205
28. Joensuu H. Acute myocardial infarction after heart irradiation in young patients with hodgkin's disease. *Chest*. 1989;95:388-390

29. Annest LS, Anderson RP, Li W, Hafermann MD. Coronary artery disease following mediastinal radiation therapy. *J Thorac Cardiovasc Surg*. 1983;85:257-263
30. Chronowski GM, Wilder RB, Tucker SL, et al. Analysis of in-field control and late toxicity for adults with early-stage hodgkin's disease treated with chemotherapy followed by radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;55:36-43
31. 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;191:32-37
32. Piovaccari G, Ferretti RM, Prati F, et al. Cardiac disease after chest irradiation for hodgkin's disease: Incidence in 108 patients with long follow-up. *Int J Cardiol*. 1995;49:39-43
33. Murabito JM, Evans JC, Larson MG, Levy D. Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation. *Circulation*. 1993;88:2548-2555
34. Apter S, Shemesh J, Raanani P, et al. Cardiovascular calcifications after radiation therapy for hodgkin lymphoma: Computed tomography detection and clinical correlation. *Coron Artery Dis*. 2006;17:145-151
35. Zinzani PL, Gherlinzoni F, Piovaccari G, et al. Cardiac injury as late toxicity of mediastinal radiation therapy for hodgkin's disease patients. *Haematologica*. 1996;81:132-137
36. Veeragandham RS, Goldin MD. Surgical management of radiation-induced heart disease. *Ann Thorac Surg*. 1998;65:1014-1019
37. Orzan F, Brusca A, Conte MR, Presbitero P, Figliomeni MC. Severe coronary artery disease after radiation therapy of the chest and mediastinum: Clinical presentation and treatment. *Br Heart J*. 1993;69:496-500
38. McEniery PT, Dorosti K, Schiavone WA, Pedrick TJ, Sheldon WC. Clinical and angiographic features of coronary artery disease after chest irradiation. *Am J Cardiol*. 1987;60:1020-1024
39. Handa N, McGregor CG, Danielson GK, et al. Coronary artery bypass grafting in patients with previous mediastinal radiation therapy. *J Thorac Cardiovasc Surg*. 1999;117:1136-1142
40. Hoving S, Heeneman S, Gijbels MJ, et al. Single-dose and fractionated irradiation promote initiation and progression of atherosclerosis and induce an inflammatory plaque phenotype in apoe(-/-) mice. *Int J Radiat Oncol Biol Phys*. 2008;71:848-857
41. Carver JR, Shapiro CL, Ng A, et al. American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. *J Clin Oncol*. 2007;25:3991-4008

42. Miltenyi Z, Keresztes K, Garai I, et al. Radiation-induced coronary artery disease in hodgkin's disease. *Cardiovasc Radiat Med*. 2004;5:38-43
43. Jurado J, Thompson PD. Prevention of coronary artery disease in cancer patients. *Pediatr Blood Cancer*. 2005;44:620-624
44. Chen AB, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost effectiveness and screening interval of lipid screening in hodgkin's lymphoma survivors. *J Clin Oncol*. 2009;27:5383-5389
45. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the american diabetes association and the european association for the study of diabetes. *Diabetes Care*. 2009;32:193-203
46. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The jnc 7 report. *JAMA*. 2003;289:2560-2572
47. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. *Circulation*. 2004;110:227-239
48. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of hodgkin's disease in children and adolescents. *J Clin Oncol*. 1993;11:1208-1215
49. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the childhood cancer survivor study cohort. *BMJ*. 2009;339:b4606
50. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. *Radiat Res*. 2003;160:381-407
51. Brosius FC, 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med*. 1981;70:519-530
52. Myrehaug S, Pintilie M, Yun L, et al. A population-based study of cardiac morbidity among hodgkin lymphoma patients with preexisting heart disease. *Blood*. 2010;116:2237-2240
53. Http://seer.Cancer.Gov/statfacts/html/hodg.Html?Statfacts_page=hodg.Html&x=12&y=15.
54. Girinsky T, Cordova A, Rey A, et al. Thallium-201 scintigraphy is not predictive of late cardiac complications in patients with hodgkin's disease treated with mediastinal radiation. *Int J Radiat Oncol Biol Phys*. 2000;48:1503-1506

55. Constine LS, Schwartz RG, Savage DE, King V, Muhs A. Cardiac function, perfusion, and morbidity in irradiated long-term survivors of hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1997;39:897-906
56. 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;22:3139-3148
57. Becker A, Leber A, Becker C, Knez A. Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. *Am Heart J*. 2008;155:154-160
58. Schmermund A, Erbel R, Silber S. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. *Am J Cardiol*. 2002;90:168-173
59. Greenland P, Bonow RO, Brundage BH, et al. Accf/aha 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the american college of cardiology foundation clinical expert consensus task force (accf/aha writing committee to update the 2000 expert consensus document on electron beam computed tomography) developed in collaboration with the society of atherosclerosis imaging and prevention and the society of cardiovascular computed tomography. *J Am Coll Cardiol*. 2007;49:378-402
60. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology*. 2003;228:826-833
61. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol*. 2003;42:743-749
62. Glanzmann C, Huguenin P, Lutolf UM, et al. Cardiac lesions after mediastinal irradiation for hodgkin's disease. *Radiother Oncol*. 1994;30:43-54
63. Greenfield DM, Wright J, Brown JE, et al. High incidence of late effects found in hodgkin's lymphoma survivors, following recall for breast cancer screening. *Br J Cancer*. 2006;94:469-472
64. Lund MB, Ihlen H, Voss BM, et al. Increased risk of heart valve regurgitation after mediastinal radiation for hodgkin's disease: An echocardiographic study. *Heart*. 1996;75:591-595
65. Nishimura RA, Carabello BA, Faxon DP, et al. Acc/aha 2008 guideline update on valvular heart disease: Focused update on infective endocarditis: A report of the american college of cardiology/american heart association task force on practice guidelines: Endorsed by the society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, and society of thoracic surgeons. *Circulation*. 2008;118:887-896

66. Bonow RO, Carabello BA, Kanu C, et al. Acc/aha 2006 guidelines for the management of patients with valvular heart disease: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease): Developed in collaboration with the society of cardiovascular anesthesiologists: Endorsed by the society for cardiovascular angiography and interventions and the society of thoracic surgeons. *Circulation*. 2006;114:e84-231
67. Chang AS, Smedira NG, Chang CL, et al. Cardiac surgery after mediastinal radiation: Extent of exposure influences outcome. *J Thorac Cardiovasc Surg*. 2007;133:404-413
68. Handa N, McGregor CG, Danielson GK, et al. Valvular heart operation in patients with previous mediastinal radiation therapy. *Ann Thorac Surg*. 2001;71:1880-1884
69. Wethal T, Lund MB, Edvardsen T, et al. Valvular dysfunction and left ventricular changes in hodgkin's lymphoma survivors. A longitudinal study. *Br J Cancer*. 2009;101:575-581
70. Lund MB, Kongerud J, Boe J, et al. Cardiopulmonary sequelae after treatment for hodgkin's disease: Increased risk in females? *Ann Oncol*. 1996;7:257-264
71. Carlson RG, Mayfield WR, Normann S, Alexander JA. Radiation-associated valvular disease. *Chest*. 1991;99:538-545
72. Applefeld MM, Wiernik PH. Cardiac disease after radiation therapy for hodgkin's disease: Analysis of 48 patients. *Am J Cardiol*. 1983;51:1679-1681
73. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; the task force on the diagnosis and management of pericardial diseases of the european society of cardiology. *Eur Heart J*. 2004;25:587-610
74. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: Etiology and cause-specific survival after pericardiectomy. *J Am Coll Cardiol*. 2004;43:1445-1452
75. Karram T, Rinkevitch D, Markiewicz W. Poor outcome in radiation-induced constrictive pericarditis. *Int J Radiat Oncol Biol Phys*. 1993;25:329-331
76. Seifert FC, Miller DC, Oesterle SN, et al. Surgical treatment of constrictive pericarditis: Analysis of outcome and diagnostic error. *Circulation*. 1985;72:II264-273
77. Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation*. 2003;108:1852-1857
78. Stewart JR, Fajardo LF. Radiation-induced heart disease: An update. *Prog Cardiovasc Dis*. 1984;27:173-194
79. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: A surgical and autopsy study of 27 cases. *Hum Pathol*. 1996;27:766-773
80. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I. Diastolic dysfunction after mediastinal irradiation. *Am Heart J*. 2005;150:977-982

81. Lee PJ, Mallik R. Cardiovascular effects of radiation therapy: Practical approach to radiation therapy-induced heart disease. *Cardiol Rev*. 2005;13:80-86
82. Adams MJ, Lipshultz SE, Schwartz C, et al. Radiation-associated cardiovascular disease: Manifestations and management. *Semin Radiat Oncol*. 2003;13:346-356
83. Green DM, Gingell RL, Pearce J, Panahon AM, Ghoorah J. The effect of mediastinal irradiation on cardiac function of patients treated during childhood and adolescence for hodgkin's disease. *J Clin Oncol*. 1987;5:239-245
84. Slama MS, Le Guludec D, Sebag C, et al. Complete atrioventricular block following mediastinal irradiation: A report of six cases. *Pacing Clin Electrophysiol*. 1991;14:1112-1118
85. Martin JD, Buckley AR, Graeb D, et al. Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. *Int J Radiat Oncol Biol Phys*. 2005;63:1197-1205
86. Dorresteijn LD, Kappelle AC, Scholz NM, et al. Increased carotid wall thickening after radiotherapy on the neck. *Eur J Cancer*. 2005;41:1026-1030
87. King LJ, Hasnain SN, Webb JA, et al. Asymptomatic carotid arterial disease in young patients following neck radiation therapy for hodgkin lymphoma. *Radiology*. 1999;213:167-172
88. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of hodgkin lymphoma. *J Natl Cancer Inst*. 2009;101:928-937

3 Arterial stiffness is increased in Hodgkin lymphoma survivors treated with radiotherapy

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Leukemia and Lymphoma; 2012 Dec. 24 [Epub ahead of print]

Abstract

Radiotherapy has been associated with an increased risk for cardiovascular disease (CVD) in Hodgkin lymphoma survivors (HLS). Identifying subjects most likely to develop these complications is challenging. Arterial stiffness has been frequently used as an early marker of CVD, but was never investigated in patients treated with radiotherapy.

Methods and results

The carotid-femoral pulse wave velocity (PWV) and the distensibility coefficient (DC) of the common carotid artery were used as markers of arterial stiffness. 82 HLS and 40 age and gender matched control subjects were studied. Aorta and the carotid arteries were situated within the radiation field in 50 and 39 patients. Mean PWV was not significantly different in HLS treated with radiotherapy on the mediastinum when compared to HLS treated without mediastinal radiotherapy and to controls. If HLS were 40years or older at radiotherapy their PWV was significantly higher (8.54m/s) than patients irradiated at younger age (7.14m/s, $p=0.004$) and controls (6.91m/s, $p<0.001$), after adjusting for current age and other CVD risk factors.
Mean DC was lower, indicative of stiffer arteries, in HLS treated with radiotherapy on the common carotid artery (2.79) than HLS without radiotherapy (3.35, $p=0.029$) and versus controls (3.60, $p=0.001$). DC was lowest in HLS treated at 35years of age or later (2.05), compared to HLS irradiated at younger age (2.98, $p=0.046$).

Conclusion

In HLS radiotherapy is associated with increased arterial stiffness. The effect of radiotherapy seems most evident when RT is administered at ages above 35-40years.

Introduction

As treatment modalities have advanced over the past decades, the number of long-term cancer survivors is increasing. These patients have significant long term morbidity related to their cancer therapy, cardiovascular (CV) events being the leading non-malignant cause of death.[1] Of all cancer treatments, radiotherapy (RT) has been mostly associated with the development of arterial disease, as frequently investigated in Hodgkin lymphoma survivors (HLS).[2] Most previous studies in HLS have concentrated on clinical end-points, showing a 30-year cumulative incidence of myocardial infarction and stroke of 12.9% and 7% respectively. [1, 3] Traditional risk factors for CV disease (diabetes, hypertension, hypercholesterolemia, smoking, positive family history) increase the risk of developing myocardial infarction or stroke in HLS.[4] However, HLS with RT as the only risk factor have been reported to develop CV events as well.[5] This makes it difficult to identify the subgroup of HLS having the highest CV risk.

In other high risk populations like patients with diabetes and chronic kidney disease, arterial stiffness has been identified as an early marker of cardiovascular disease and a surrogate marker for cardiovascular mortality.[6] The aortic pulse wave velocity (PWV) and the carotid distensibility coefficient (DC) are frequently used parameters to measure arterial stiffness.[6] So far there are no studies investigating arterial stiffness and its relation with cardiovascular morbidity and mortality in survivors of radiation treatment. The aim of our study is to evaluate arterial stiffness in HLS treated with and without RT, compared to control subjects.

Materials and methods

Participants

Between November 2007 and August 2008, 122 participants were enrolled in this study: 82 HLS and 40 age and gender matched control individuals. The control population consisted of randomly selected spouses of patients. This study was approved by the review committee of our institution and all subjects gave informed consent. At our institution all patients previously treated for HL are monitored at regular intervals by their hematologist to detect recurrences of HL or long-term treatment complications. All HLS registered at our institution who were

free of disease and had a follow-up from diagnosis of HL of more than 2 years were invited to participate in the current study (n=113). Nineteen HLS had died; the cause of death could be retrieved in 11 patients: seven suffered from a secondary malignancy, three from cardiovascular complications and one died from an infectious complication. Six HLS did not attend their regular check-ups and could not be traced. Another six HLS declined participation because of old age (n=3), long travelling distance (n=1) or without a specific reason (n=2). The patients who declined participation were slightly older than the included subjects (mean age 57 ±17 years) but did not differ in terms of treatment characteristics.

Patients were treated between 1969 and 2005 with different regimens. Typically extended field radiotherapy (mostly mantle field RT to the neck, mediastinum, axillary lymph nodes and sometimes para-aortic lymph nodes) was performed in patients with limited stage HL until the late 1990's, being replaced by involved field radiation in the more recently treated patients. HLS with more advanced stages were primarily treated with chemotherapy (CT) to which radiotherapy was added in case of bulky disease, mostly located in the mediastinum. Recently CT and RT were combined in most patients (Figure 1). The radiation dose was 40Gy in fractions of 2 Gy when RT was the only treatment and 30-36 Gy when RT was combined with CT.

Until the 1980's the CT consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were introduced as a part of the primary treatment.

Data was collected on the CV history and CV risk factors. Body mass index (BMI) and abdominal circumference were measured. Furthermore a blood sample was drawn after overnight fasting for determination of glucose, HbA1C and lipid profile.

Arterial Stiffness Measurements

Prior to measurements the participants were asked to rest supine in a quiet room for ten minutes. Blood pressure (BP) was recorded before every PWV and DC measurements. BP was measured using an automatic oscillometric device (Model MX3 Plus, Omron Matsusaka, Tokyo, Japan). All measurements were done by one researcher in the same room, blinded for the initial treatment of the HLS. Mean BP was calculated by using the formula 0.4(systolic BP - diastolic BP) + diastolic BP.[7] The SphygmoCor device (Model SCOR-Px, Software version, 7.01, AtCor

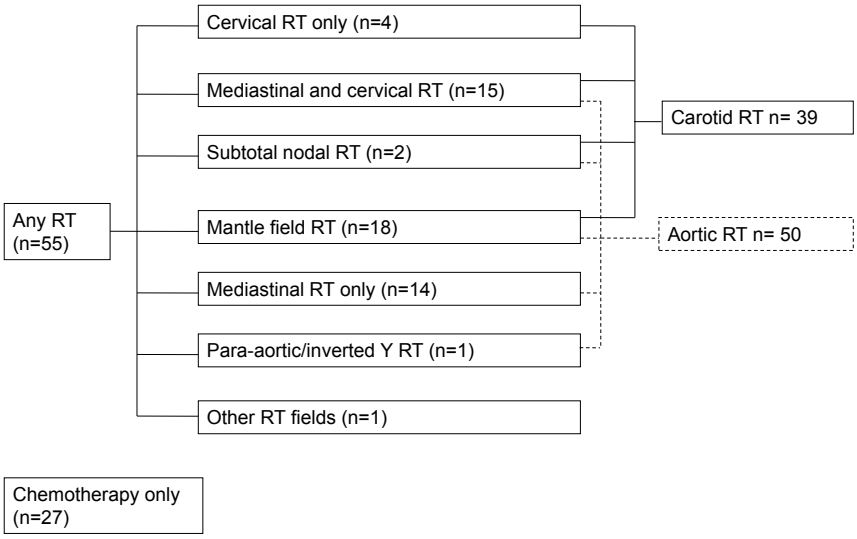

Figure 1. Treatment modalities in 82 Hodgkin lymphoma survivors

Medical Pvt. Ltd, Sydney, Australia) equipped with a tonometric Millar transducer was used to determine the aortic PWV. The pulse wave was recorded sequentially at the femoral artery and at the carotid artery. A simultaneously recorded electrocardiogram (ECG) is used as a reference to calculate wave transit time. Transit time between carotid and femoral pressure waves is calculated by recording duration from R-wave to intersection tangent of pulse wave arrival to the carotid or femoral sites during 10 heart beat cycles. Two surface distances are measured by the investigator: between the recording point at the carotid artery and the sternal notch (distance 1) and between the sternal notch and the recording point at the femoral artery (distance 2). The distance travelled by the pulse wave (DPW) is calculated by the SphygmoCor as (distance 2) - (distance 1). The PWV is then calculated as PWV = DPW (m) / transit time (s). We have described this technique in detail elsewhere.[8] Higher PWV is indicative of stiffer arteries.

Arterial stiffness was assessed by measurement of distension of the right and left common carotid arteries. The distension of an artery is the change in diameter in systole relative to the diastolic diameter during the cardiac cycle. A 9-3 MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (Philips IU22) was

used to record the ultrasound images. After a rest of at least 5 minutes, patients were examined in supine position with the head turned approximately 45 degrees away from the side examined. Longitudinal B-mode images were obtained of the left and right common carotid arteries, immediately proximal to the carotid bifurcation. The sonographer adjusted focus and gain settings to optimise far-wall echoes and to minimise noise in the arterial lumen. The end-diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter (ΔD/D) were computed. The cross-sectional arterial wall DC was calculated according to the following equation: DC= 2(ΔD/D)/pulse pressure (10^{-3}/mmHg). Lower DC is indicative of stiffer arteries.

Statistics

The two primary outcome measures required a different grouping of the HLS cohort at analysis, as the PWV and DC are markers of arterial stiffness at the aorta and common carotid artery (CCA) respectively. In order to analyze the PWV, the total group of HLS was divided in patients in whom the radiation field included the aorta (RT_{aorta}+, n= 50 HLS) and patients in whom it did not include the aorta (RT_{aorta}−, n=32 HLS).Similarly, for DC analysis the following groups were defined: RT_{CCA}+ (n=39 HLS) and RT_{CCA}− (n=43 HLS), according to whether the CCA was included or not in the radiation field (Figure 1).

DC was measured in the right and left CCA, as eight patients had been treated with unilateral RT. To account for this intra-individual variation, we used linear mixed models with a random intercept per patient when analyzing the DC as an outcome variable. PWV was analyzed using linear regression.

In order to determine which parameters were predictors of DC or PWV, models containing only one predictor were fitted for the HLS and control groups separately. First we examined traditional CV risk factors (age, male gender, cholesterol, glucose, blood pressure, smoking, abdominal circumference, BMI, current use of blood pressure or cholesterol lowering medication, family history of CV disease), differentiating between HLS and controls in order to compare the effect of these risk factors in these two groups. Characteristics of HL treatment (age at diagnosis, follow-up since diagnosis, RT dose) were compared between HLS treated with and without RT. We used the RT dose as a categorical variable (eg. RT_{aorta} dose <= 36Gy (n=12) and RT_{aorta} >36Gy (n=38)) since it was not normally distributed.

In the simple linear regression analysis, age at diagnosis of HL (age_{HL}) proved to be a variable associated with both DC and PWV; for obvious reasons, this variable cannot be defined for the control subjects. To deal with this problem we created a grouping variable combining RT_{aorta}+/ RT_{aorta}− (or RT_{CCA}+/ RT_{CCA}−) and a dichotomized age at diagnosis of HL (age_{HL}). This resulted in five groups: controls, patients diagnosed before the cut-off age and RT+, patients diagnosed before the cut-off age and RT-, patients diagnosed after the cutoff age and RT+, and patients diagnosed after the cutoff age and RT-. Choosing the cut-off point was performed by analyzing which age_{HL} best predicted the PWV or DC respectively. For PWV, age was dichotomized at 40 years, and for DC at 35 years. The reason that 40 years was not chosen as a cut-off point for the DC is that only 5 patients were irradiated on the neck at 40 years of age or older which resulted in a less solid association with the DC for the first group.

Finally, a multiple regression model was fitted for PWV and a multiple linear mixed model for DC. Both models included the following variables: current age, gender, the RT_{aorta} / RT_{CCA} and age_{HL} group, mean BP, current use of cholesterol lowering medication, HDL, LDL, family history of CV disease, pack years of smoking, current use of blood pressure lowering medication. From the multiple regression models, adjusted mean PWV or DC was estimated for the different RT/age groups, and those means were compared using the Bonferroni-adjusted post-hoc tests.

Results

Base line characteristics of the study population are described in Table I.

Pulse Wave Velocity

Pulse wave velocity did not differ significantly the RT_{aorta}+ group vs. RT_{aorta}− group vs. controls: means (95% CI) 7.3 m/s (6.9−7.8) vs. 7.1 m/s (6.6−7.7) and 6.6 m/s (6.2−7.1) respectively. In unadjusted analysis, traditional risk factors for cardiovascular disease were better predictors of PWV in the control group compared to the entire HLS group (Table II). The parameter estimate indicates, for example, that in the entire HLS group, the PWV increases with increasing age, by 0.09m/s for every year. For categorical variables, the parameter estimate should be inter-

preted as follows, for example, the PWV increases if the subject uses BP lowering medication, by 1.56m/s if the patient uses BP lowering medication versus non-users.
Age at diagnosis was the only treatment related factor associated with PWV in univariate analysis; RT to the aorta, RT dose and chemotherapy were not significant predictors (Table III). In the multiple linear regression model the following variables were still significant predictors of PWV: current age, the RT_{aorta} and age_{HL} group and mean BP (Table IV). If we included gender and the traditional risk factors in the multivariate model as confounders, PWV was highest in the RT_{aorta}+ and age_{HL}≥40 group. (Figure 2)

Carotid Artery Distensibility

The mean (95%CI) DC was lowest in the RT_{CCA}+ group: 2.79 (2.47−3.11) and differed significantly (p=0.029) from the RT_{CCA}− group, mean 3.35 (3.08−3.62) and controls (p=0.001), mean 3.59 (3.28−3.91). In the unadjusted analysis, traditional risk factors for cardiovascular disease were better predictors of DC in the control group compared to HLS. (Table II). The parameter estimate should be interpreted in the opposite way for the DC since a lower DC is indicative of stiffer arteries (in contrast to higher PWV indicative of stiffer arteries). For example, in the entire HLS group, the DC decreases with increasing age, by $0.07x10^{-3}$/mmHg for every year, etc.
RT to the neck and age at diagnosis were the only treatment related factors associated with DC in univariate analysis; RT dose and chemotherapy were not significant predictors (Table III). In the full linear mixed model the following variables were still significant predictors of DC: current age, mean BP, the RT_{CCA} and age_{HL} group (Table IV). If we included gender and the traditional risk factors in the multivariate model as confounders, DC was lowest in the RT_{CCA}+ and age_{HL}≥35 group. (Figure 3) Furthermore present use of cholesterol lowering medication became significant in the adjusted model, showing a protective effect on DC.

Table I. Baseline characteristics.

BP Blood pressure, BMI body mass index, CCA common carotid artery, CVD cardiovascular disease.

	Hodgkin Lymphoma survivors n=82				Control subjects n=40
	Radiotherapy on the aorta n= 50	No radiotherapy on the aorta n= 32	Radiotherapy on the CCA n= 39	No radiotherapy on the CCA n= 43	
Male (number)	26	19	20	25	22
Age (mean)	48	48	46.5	49	48
BMI (kg/m2)	24.8	27.6	24.4	27.2	26.1
Abdominal circumference (cm)	93	100	92	99	96
Positive family history of CVD	12	5	11	6	10
Smoking (pack years)	4.9	11.4	5.4	9.3	4.8
Glucose (mmol/l)	5.5	5.4	5.6	5.4	5.1
HbA1C (%)	5.7	5.6	5.7	5.6	5.5
HDL cholesterol (mmol/l)	1.53	1.36	1.53	1.41	1.41
LDL cholesterol (mmol/l)	3.05	3.07	3.08	3.04	3.19
Current use of cholesterol lowering medication (n)	10	8	14	4	2
Mean BP (mmHg)	97.6	100.1	96.7	100.3	95.4
Current use of BP lowering medication (n)	9	7	7	9	3
Age at diagnosis (mean)	30.2	38.5	29.3	37.2	-
Time since diagnosis (mean)	16.6	8.0	16.1	10.7	-

Table II. Univariate association of traditional risk factors and arterial stiffness indicators in HLS and control subjects.

	Hodgkin lymphoma survivors				Controls			
Risk factor	Parameter Estimate	95% CI		p	Parameter Estimate	95% CI		p
Pulse wave velocity (m/s)								
Current age, years	0.09	0.07	0.11	.000	0.06	0.04	0.09	.000
Gender, male	-0.25	-0.97	-0.46	NS	-0.24	-1.11	-0.63	NS
Mean BP, mmHg	0.07	0.04	0.09	.000	0.07	0.04	0.11	.000
BP lowering medication	1.56	0.70	2.41	.000	1.53	0.17	2.89	.029
HDL-c, mmol/l	-0.64	-1.53	0.24	NS	-1.18	-2.27	-0.09	.035
LDL-c, mmol/l	-0.09	-0.49	0.32	NS	0.82	0.28	1.37	.004
Smoking (pack years)	0.03	0.01	0.06	.016	0.06	0.01	0.11	.014
Abdominal circumference (cm)	0.04	0.02	0.07	.002	0.04	0.00	0.08	.049
Cholesterol lowering medication	1.34	0.59	2.08	.001	1.99	0.47	3.50	.012
Distensibility coefficient (10^{-3}/mmHg)								
Current age,years	-0.07	-0.08	-0.05	.000	-0.07	-0.09	-0.05	.000
Gender, male	-0.00	-0.57	0.57	NS	-1.00	-1.79	-0.23	.012
Mean BP, mmHg	-0.03	-0.05	-0.01	.001	-0.07	-0.1	-0.04	.000
Heart rate, bpm	-0.02	-0.37	-0.04	.016	0.04	-0.00	0.91	NS
BP lowering medication.	-1.29	-1.94	-0.63	.000	-1.17	-2.51	0.18	NS
HDL-c, mmol/l	0.05	-0.64	0.74	NS	1.12	0.05	2.18	.040
LDL-c, mmol/l	0.16	-0.17	0.48	NS	-0.65	-1.20	-0.10	.022
Smoking (pack years)	-0.03	-0.40	-0.01	.013	-0.05	-0.1	-0.01	.027
Abdominal circumference (cm)	-0.03	-0.05	-0.01	.010	-0.07	-0.10	-0.03	.000
Familly history of CVD	-0.03	-0.99	0.32	NS	-1.36	-2.19	-0.52	.002

Table III. Univariate association of HL treatment related factors and arterial stiffness indicators in HLS.

	Hodgkin lymphoma survivors							
	$RT_{aorta/CCA+}$				$RT_{aorta/CCA-}$			
Treatment related factor	Parameter Estimate	95% CI		p	Parameter Estimate	95% CI		p
Pulse wave velocity (m/s)								
Radiotherapy on the aorta	0.19	-0.54	0.92	NS	reference			
Age at diagnosis, years	0.085	0.06	0.11	.000	0.06	0.03	0.10	.001
Distensibility coefficient (10^{-3}/mmHg)								
Radiotherapy on the neck	-0.60	-1.00	-0.19	.004	reference			
Follow-up since HL, years	-0.02	-0.07	0.02	NS	-0.06	-0.10	-0.01	.025
Age at diagnosis, years	-0.07	-0.10	-0.05	.000	-0.04	-0.06	-0.01	.003

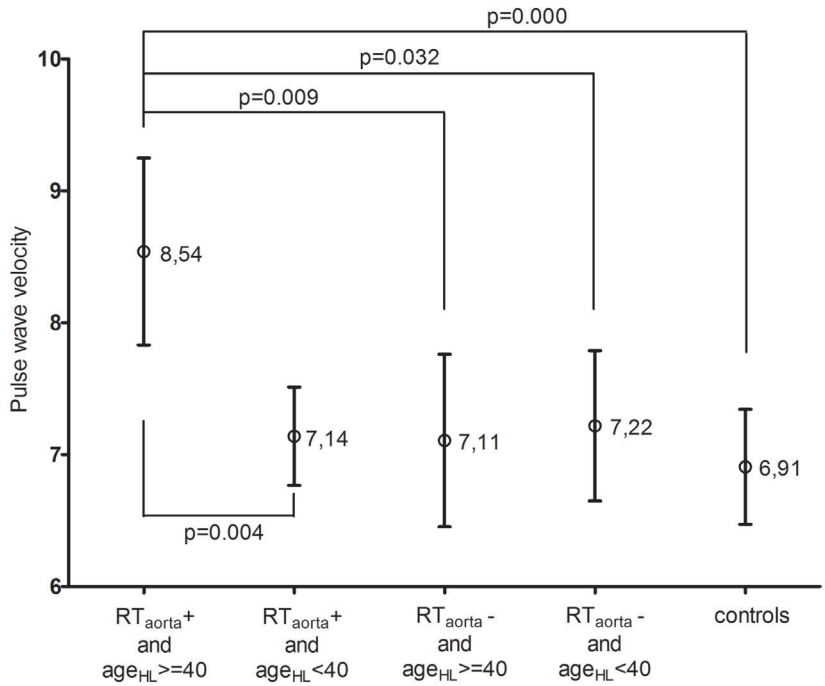

Figure 2. Adjusted means of PWV (in m/s) after fitting a general linear regression model including current age, gender, the RTaorta and ageHL group, mean BP, current use of BP lowering medication., HDL, LDL, family history of CVD, pack years of smoking, current use of cholesterol lowering medication. Covariates appearing in the model are evaluated at the following values: current age = 47,77, mean BP = 97.7, abdominal circumference = 95.8, pack years of smoking = 6.6, HDL = 1.44, LDL = 3.1. All subgroups were compared with each other. Only statistically significant results are shown in the figure.

Tabel IV. Multivariable association of factors related to DC and PWV in HLS treated with or without RT on the carotid arteries.

Pulse wave velocity (m/s) Multiple general linear model with PWV as dependent variable					
	Parameter estimate	95% CI		p value	F
Current age	0.05	0.03	0.07	.000	20.2
Mean BP, mmHg	0.04	0.03	0.06	.000	25.7
RT_{CCA} and age_{HL} group					5.1
RT_{aorta}+ and age_{HL}≥40	1.63	0.90	2.37	.000	
RT_{aorta}+ and age_{HL}<40	0.23	-0.24	0.71	NS	
RT_{aorta}− and age_{HL}≥40	0.20	-0.47	0.87	NS	
RT_{aorta}− and age_{HL}<40	0.31	-0.27	0.89	NS	
controls	ref.				
Distensibility coefficient (10^{-3}/mmHg) Multiple mixed linear model with DC as dependent variable					
	Parameter estimate	95% CI		p value	F
Current age	-0.05	-0.07	-0.04	.000	40.5
Mean BP, mmHg	-0.02	-0.04	-0.01	.000	12.7
RT_{CCA} and age_{HL} group					8.1
RT_{CCA}+ and age_{HL}≥35	-1.56	-2.15	-0.97	.000	
RT_{CCA}+ and age_{HL}<35	-0.62	-1.05	-0.19	.005	
RT_{CCA}− and age_{HL}≥35	-0.14	-0.60	0.32	.547	
RT_{CCA}− and age_{HL}<35	-0.30	-0.71	0.12	.164	
controls	ref.				
Cholesterol lowering medication	0.49	0.06	0.91	.024	5.2

Discussion

In the present study, arterial stiffness was evaluated in a group of HLS and their age and gender matched controls. Arterial stiffening was found in HLS treated with RT when compared to controls and to HLS who were not treated with RT. This finding is most evident in HLS treated at older age (>35-40 years). This is in agreement with a large retrospective trial in which older patients at RT had the highest risk of MI and stroke. They developed these cardiovascular end-points earlier than HLS treated at younger age [4]. Similarly, the 15-year cumulative incidence of a cardiac hospitalization was estimated to be higher for HLS treated at age 40 versus age 20 (1.8% compared to 16.5%). [9] Large cohort studies have reported that the relative risk of MI and stroke decreases with increasing age at diagnosis, finding that probably reflects the lower background risk of CVD at younger age. [1, 3, 10] However, these studies also found an increased absolute excess risk of these CV end-

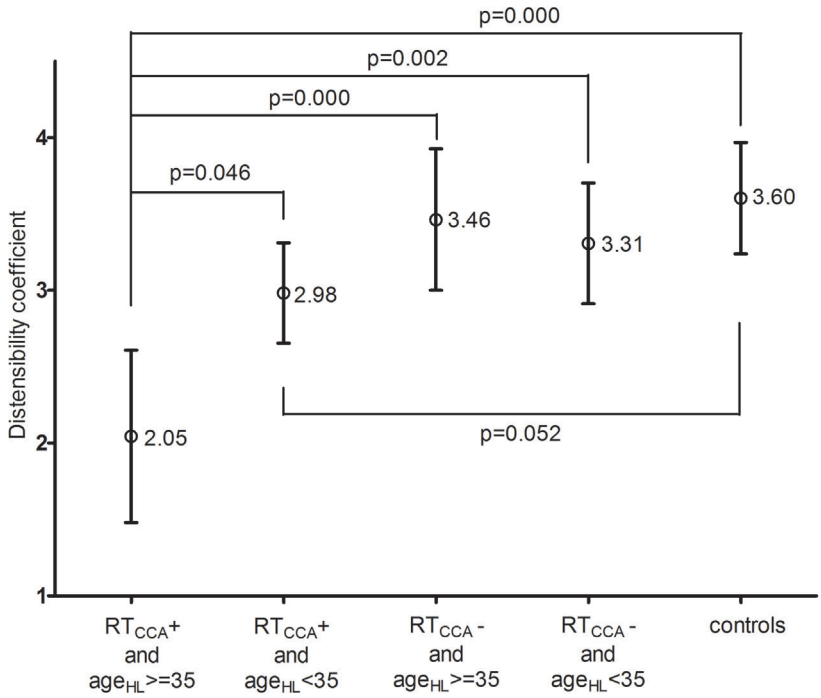

Figure 3. Adjusted means of DC (10-3/mmHg) after fitting a mixed models linear regression including current age, gender, the RTCCA and ageHL group, mean BP, current se of cholesterol lowering medication, HDL, LDL, family history of CVD, packyears of smoking, current use of blood pressure lowering medication. Covariates appearing in the model are evaluated at the following values: current age = 47.81, mean BP = 95.9, abdominal circumference = 95.7, pack years of smoking = 6.6, HDL = 1.45, LDL = 3.1. All subgroups were compared with each other. Only statistically significant results are shown in the figure.

points with increasing age at RT. [1, 3, 10] This absolute excess risk might be of greater relevance for the individual patient who has a high absolute increased risk of developing CVD if treated with RT at older age. These patients might benefit from individually tailored therapy: older patients at diagnosis, who have a high CV risk profile based on traditional RF, being best treated with CT only. Future studies are needed in to address this hypothesis.

Our paper is the first to report on RT-associated arterial stiffening. Even though many epidemiologic studies show an increased risk of manifest cardiovascular disease after RT, only few observational studies in humans have investigated early signs of RT-induced vasculopathy.

Endothelial dysfunction [11-13], increased intima media thickness (IMT) [14-15] and coronary artery calcifications [5, 16] have been described. Further follow-up studies are needed before the most valuable method of assessing CV risk in irradiated patients is defined. One earlier report in HLS showed impaired endothelial function in 26 HLS at an average of 6.7 years after mediastinal RT [13]. There was no association between endothelial dysfunction and age at treatment. This can be due to the young age at examination (12-30 years) in this study. Furthermore, even though arterial stiffness and endothelial dysfunction have been shown to be associated [17], they represent different aspects of vascular disease [18]. Although the precise relationship between arterial stiffness and endothelial dysfunction still remains to be established [19], it has been shown that endothelial dysfunction is already present at an early stage after RT [12]. Sugihara et al found that NO- and prostacyclin-mediated endothelium dysfunction was present 4-6 weeks after RT in human cervical arteries [12]. Diminished endothelium-dependent vasodilatation was still observed years after RT by Beckman et al [11].

The pathological substrate of radiation induced vascular damage has been investigated in animal studies and human autopsy studies in subjects previously treated with RT [15, 20-21]. Atherosclerotic lesions consisted mainly of fibrous tissue in intima and media in 10 patients previously treated with RT [20]. Furthermore the internal elastic membrane was disrupted in 39% of coronary artery sections in these patients [20]. Both the presence of fibrous tissue and the degeneration of the elastic fibers might result in arterial stiffening [21]. Recently, Russel et al found an increased intima-media thickness and increased proteoglycan content of the irradiated vessels [15]. These changes are known to stiffen the extracellular matrix of vessel walls [22].

Remarkably, we found that the effect of RT on arterial stiffness was stronger when patients were treated at older age. We hypothesize that nitric oxide (NO) and atherosclerosis play an important role in this RT-induced arterial stiffness in HLS treated at older age [22]. It has been shown that bioavailabilty of NO decreases with older age in healthy subjects [23]. RT also decreases the level of NO [12], possibly causing a more pronounced arterial stiffness in subjects treated with RT at older age. Atherosclerosis is associated with arterial stiffness in older healthy adults [24]. Furthermore, RT has been shown to induce or accelerate ath-

erosclerosis [25], which is increasingly present in elderly patients.
The fact that survival time (time since RT) was not related to both measurements of arterial stiffness might indicate that the effect of RT on arterial stiffness mainly occurs at the time of RT or during the first 2 years after RT. If RT induced stiffening would continue to increase at increased pace, we would have expected a relationship between the stiffness parameters and survival time. This finding could help identify patients at risk for CVD at an early stage after RT. These patients could be monitored more closely and cardiovascular risk factors could be treated more strictly, as we have found that a lower blood pressure and using cholesterol lowering medication is associated with lower arterial stiffness.
Traditional risk factors for CVD were shown to have an increased effect in the development of symptomatic CVD in HLS.[2, 4] We observed that traditional RF were stronger associated with arterial stiffness in controls than in HLS. Apparently RT has strong and overruling effect on arterial stiffness.
Results are more evident for DC than for PWV. This can be explained by the larger number of measurements, hence a higher power resulting from the double sided DC measurements. Furthermore the DC was measured in the CCA which was fully irradiated, whereas the aorta was only partially included in the radiation field. Unfortunately we were not able to determine the exact RT dose to the aorta in comparison to the common carotid artery, but a higher RT dose to the common carotid artery could also play a role in our findings. In pathological studies it was shown that larger arteries are less prone to lesions due to RT when compared to smaller diameter arteries.[21]
HLS treated without RT or with RT at younger age had comparable PWV and DC to the general population.[26-27] In the RT_{aorta}+ and age_{HL}≥40 group, PWV was 8.54m/s in the multivariable model with the current age set at 47.77 years. This value corresponds to the PWV for the 50-59 years old patients with normal blood pressure and to the 45-49 years old patients with grade 1 hypertension.[26] Similarly, DC in the RTcca+ at age >35 group was comparable with subjects who had smoked for at least 20 years.[27]
Strong points of this study are the similar results for two independent measures of large arterial stiffness: PWV and DC. The measurements of arterial stiffness were performed by an independent researcher

blinded for the initial treatment of the HLS. We have collected data on many known atherosclerosis risk factors for which we could adjust in the multivariate models. Most important weaknesses of the study are the small numbers of patients and the fact that it is an observational study in which we do not have data on arterial stiffness at the time of diagnosis and RT. Since we performed the study in patients surviving HL at least 2 years we cannot establish the acute effects of RT. The disadvantage of studying subjects at various times after RT, turns in the advantage of being able to study the effect of survival time. However, over time, the RT techniques and treatment regimens have changed. In recent years, patients with higher stage HL were no longer primarily treated with RT, but with anthracycline containing CT. As a consequence there is a different follow-up time from diagnosis in the patients treated with and without RT (Table I). In this cohort we did not find an effect of follow-up time on arterial stiffness parameters, but further studies including patients treated more recently with newer regimens are needed to confirm this finding. Another difference at baseline is the higher age at diagnosis in the patients treated without RT. This can be explained by the fact that this patient group was treated more recently and by the fact that older patients treated by old regimens (mostly including RT) deceased before we performed this cross-sectional study. Furthermore during the past years more elderly patients were diagnosed and treated for HL than before. The higher age at treatment in the non-RT group might be expected to result in stiffer arteries in this group. However, we observed the opposite. The observed increased stiffness in patients treated with RT might underestimate the true effect of RT due to this age difference.

The cohort described in this paper has been treated with older treatment regimens. The RT doses are currently as low as 20-30Gy, in comparison to 36-40Gy which were mostly used in our study population. We did not find a relationship between RT dose and arterial stiffness, but this can be due to the small variations in RT dose between patients. Moreover, anthracycline-based CT regimens are almost always used nowadays, with or without RT. In our population CT regimens included anthracyclines in 80% of the HLS treated by CT. There is evidence that these new CT regimens also increase arterial stiffness shortly (4 months) after RT. [28] Our study showed that CT does not influence the

arterial stiffness on the long term. Further investigations should be performed in long-term HLS treated with modern regimens to address these issues.

In conclusion we show that RT seems to stiffen large arteries, especially when RT is administered at ages above 35-40 years. Since follow-up time from treatment was not associated with stiffer arteries, stiffening seems to occur soon after RT. Therefore, PWV and DC could be of help to identify patients at risk of CVD. Prospective studies are needed to follow these patients and to investigate the direct relation of stiffness and CVD in patients who have undergone RT.

Acknowledgments

We thank Danny van Maurik, neurophysiologic analyst for performing of the PWV and DC measurements.

References

1. Aleman BM, van den Belt-Dusebout AW, Klokman WJ*, et al.* Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003;21:3431-3439.
2. Aleman BM, van den Belt-Dusebout AW, De Bruin ML*, et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878-1886.
3. De Bruin ML, Dorresteijn LD, van't Veer MB*, et al.* Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst* 2009;101:928-937.
4. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
5. 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;28:1025-1030.
6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318-1327.
7. Bos WJ, Verrij E, Vincent HH*, et al.* How to assess mean blood pressure properly at the brachial artery level. *J Hypertens* 2007;25:751-755.
8. van Leeuwen-Segarceanu EM, Tromp WF, Bos WJ*, et al.* Comparison of two instruments measuring carotid-femoral pulse wave velocity: Vicorder versus SphygmoCor. *J Hypertens* 2010;28:1687-1691.
9. Myrehaug S, Pintilie M, Yun L*, et al.* A population-based study of cardiac morbidity among Hodgkin lymphoma patients with preexisting heart disease. *Blood* 2010;116:2237-2240.
10. 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;99:206-214.
11. Beckman JA, Thakore A, Kalinowski BH*, et al.* Radiation therapy impairs endothelium-dependent vasodilation in humans. *J Am Coll Cardiol* 2001;37:761-765.
12. Sugihara T, Hattori Y, Yamamoto Y*, et al.* Preferential impairment of nitric oxide-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. *Circulation* 1999;100:635-641.
13. Zelcer S, Chen B, Mangel J*, et al.* Impaired vascular function in asymptomatic young adult survivors of Hodgkin Lymphoma following mediastinal radiation. *J Cancer Surviv* 2010;4:218-224.

14. Dorresteijn LD, Kappelle AC, Scholz NM*, et al.* Increased carotid wall thickening after radiotherapy on the neck. *Eur J Cancer* 2005;41:1026-1030.
15. Russell NS, Hoving S, Heeneman S*, et al.* Novel insights into pathological changes in muscular arteries of radiotherapy patients. *Radiother Oncol* 2009;92:477-483.
16. Andersen R, Wethal T, Gunther A*, et al.* Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. *Am J Cardiol* 2010;105:149-152.
17. McEniery CM, Wallace S, Mackenzie IS*, et al.* Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension* 2006;48:602-608.
18. Anderson TJ. Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. *Can J Cardiol* 2006;22 Suppl B:72B-80B.
19. Widlansky ME, Gokce N, Keaney JF, Jr.*, et al.* The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003;42:1149-1160.
20. Brosius FC, 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981;70:519-530.
21. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. *Catheter Cardiovasc Interv* 2008;72:563-568.
22. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:932-943.
23. Lyons D, Roy S, Patel M*, et al.* Impaired nitric oxide-mediated vasodilatation and total body nitric oxide production in healthy old age. *Clin Sci (Lond)* 1997;93:519-525.
24. van Popele NM, Mattace-Raso FU, Vliegenthart R*, et al.* Aortic stiffness is associated with atherosclerosis of the coronary arteries in older adults: the Rotterdam Study. *J Hypertens* 2006;24:2371-2376.
25. Stewart FA, Heeneman S, Te Poele J*, et al.* Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649-658.
26. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31:2338-2350.
27. Smilde TJ, van den Berkmortel FW, Boers GH*, et al.* Carotid and femoral artery wall thickness and stiffness in patients at risk for cardiovascular disease, with special emphasis on hyperhomocysteinemia. *Arterioscler Thromb Vasc Biol* 1998;18:1958-1963.
28. Chaosuwannakit N, D'Agostino R, Jr., Hamilton CA*, et al.* Aortic stiffness increases upon receipt of anthracycline chemotherapy. *J Clin Oncol* 2010;28:166-172.

4 Comparison of two instruments measuring carotid-femoral pulsewave velocity: Vicorder versus SphygmoCor

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Journal of hypertension 2010; 28(8):1687-1691

Abstract

Background

The carotid-femoral pulse wave velocity (PWVcf) is used as an indicator of arterial stiffness. It is often measured using applanation tonometry, for instance with the SphygmoCor. In young children this method is difficult to perform. Therefore, techniques are needed that are less dependent on patient compliance. The Vicorder device uses the oscillometric technique to measure the PWVcf and is thought to be less time consuming and less dependent on operator skills.

Objective

To compare the PWVcf measured by an extensively used device (SphygmoCor) and the Vicorder in adults initially.

Methods

38 healthy volunteers (20 men, mean age 48 ± 13.1 years) participated in this cross-sectional study. The PWVcf was assessed twice using the SphygmoCor and the Vicorder by a single investigator during one visit. Intra-rater reproducibility of each instrument and comparison between the two instruments were assessed by the Bland-Altman method.

Results

The mean difference [95% Confidence Interval] between repeated measurements was 0.09 [-0.20 – 0.38] m/s and 0.24 [-0.55 – 1.03] m/s, for the SphygmoCor and Vicorder, respectively. The Limits of Agreement (LoA) were -1.53 – 1.71 m/s and -4.24 – 4.72 m/s, for the SphygmoCor and Vicorder, respectively. The mean PWVcf measured by the Vicorder was 0.58 [-0.20 – 1.35] m/s higher than the PWVcf measured by the SphygmoCor. The LoA between the two instruments were -3.50 – 4.66 m/s.

Conclusions

The LoA of both instruments exceed a value of 1.5m/s. The LoA of the Vicorder PWVcf measurements are considered too wide for using this technique reliably in adults or in children.

Introduction

Carotid-femoral PWV (PWVcf) is nowadays considered the 'gold-standard' indicator of arterial stiffness.[1] PWVcf has been demonstrated to be a strong predictor of cardiovascular mortality in various patient populations, especially in patients with End Stage Renal Disease (ESRD).[2] In children and young adults with ESRD the mortality is mainly due to cardiovascular disease.[3] Therefore, PWVcf measurement might be a valid indicator of the extent of vascular damage in this patient group and could be used to identify patients at higher risk of cardiovascular disease.

Measuring the PWV over the carotid-femoral trajectory has been considered the gold standard in a recent guideline.[1] Various non-invasive techniques have been used[4] like computerized oscillometry[5], tonometry (SphygmoCor)[6], ultrasound[7-8] and methods using mechanotransducers (Complior)[9]. There is no consensus about which measurement method is the most valid and reliable.[4] This is why there is room for new instruments to enter the market and be promoted by their producers as a valid instrument for measuring the PWVcf.

The SphygmoCor is an instrument using applanation tonometry that has been extensively used, is easily applied in adults and has a fair reproducibility.[10-11] However, we noticed that in young children the measurements by the SphygmoCor are often difficult to carry out as they are time consuming and require some degree of patient cooperation. Therefore we searched for a new device that is better applicable in children.

The Vicorder is a new automatic device that was originally used to measure differences in blood pressure like the ankle-brachial index.[12] It has been adapted to measure the PWVcf by adding a neck pad which is placed over the carotid artery. The Vicorder uses the oscillometric technique to measure the PWVcf, through the inflation of this neck pad and a cuff around the thigh. It is presented as a simple and quick non-invasive method which is little dependent on operator skills and experience.

Before investigating the clinimetric properties of the Vicorder in children, we decided to test the validity of the instrument in adults. For the Vicorder to be valid, we consider it necessary that its measurements are reproducible, i.e., differences between repeated measurements

without clinically relevant change in the subject should be reasonably small, and the measurements should be comparable to measurements made by the Sphygmocor. To this purpose, we compared the Vicorder with the SphygmoCor in a group of adults in an ongoing study. The precise aims of the current study are the following:
to compare the test-retest reproducibility of the PWVcf measurements with the SphygmoCor and the Vicorder; and
to investigate the comparability of the PWVcf measurements with both instruments.

Methods

Participants

The HORCIA study is a single centre cohort study to detect late sequelae of radio- and chemotherapy in survivors of Hodgkin lymphoma. To detect preclinical markers of cardiovascular disease, PWVcf measurements with the SphygmoCor are performed in all patients. Forty spouses of the patients were randomly selected and asked to participate as control subjects. These control subjects also underwent PWVcf measurements in order to have reference values for their spouses. These volunteers were invited to participate in the present cross-sectional study. Ethical approval has been given by the Institutional Review Board of the St. Antonius hospital in Nieuwegein.

Technique

All participants were measured twice with both devices during a single visit. The measurements were performed as described in the manual of each device. Prior to the measurements the participants took 10 minutes of rest lying supine in a quiet room. Blood pressure (BP) was measured before each PWVcf measurement. The BP was measured using an automatic oscillometric device (Model MX3 Plus, Omron Matsusaka, Tokyo, Japan). All measurements were done by one researcher in the same room. The order of PWVcf measurements was as follows: Vicorder1, SphygmoCor1, SphygmoCor2 and Vicorder2.

SphygmoCor

The SphygmoCor (Model SCOR-Px, Software version, 7.01, AtCor Medical Pvt. Ltd, Sydney, Australia) uses a single high-fidelity tonometric

Millar transducer. To determine the PWVcf, the pulse wave is recorded sequentially at the femoral artery and at the carotid artery by the transducer. A simultaneously recorded electrocardiogram (ECG) is used as a reference to calculate wave transit time. Transit time between carotid and femoral pressure waves is calculated using the 'foot-to-foot' method. Wave 'feet' are identified using intersecting tangent algorithms. Two surface distances are measured by the investigator: between the recording point at the carotid artery and the sternal notch (distance 1) and between the sternal notch and the recording point at the femoral artery (distance 2). The distance travelled by the pulse wave (DPW) is calculated by the SphygmoCor as (distance 2) - (distance 1). The PWVcf is then calculated as PWVcf = DPW (m) / transit time (s). To assure good quality of the measurements, the following rules, as described previously, were taken into account:
Visually acceptable pulse-waveforms and a mean pulse height above 80mV were required and the time difference between the ECG-signal and the signal from the recording sites should have an SD of less than 10% of the mean value.[10]

Vicorder

The Vicorder (Skidmore Medical Limited, Bristol, United Kingdom) is a new device that received FDA approval on December 20th 2007.[12] The Vicorder simultaneously records the pulse wave from the carotid and femoral site by using the oscillometric method. First a neck pad which is only inflatable over several centimetres is placed around the patient's neck. This pressure pad is applied over the right carotid artery to prevent compression of the trachea and compression of both carotid arteries at the same time. Next a cuff is placed around patient's right upper thigh. Both carotid and femoral cuffs are inflated automatically to 65mmHg and the corresponding oscillometric signal from each cuff is digitally analyzed to extract, in real time, the pulse time delay. After acquiring several steady pulses the investigator "freezes" the recording on the display and the Transit Time in milliseconds is presented. DPW is measured as follows: DPW = the distance between the upper edge of the femoral cuff and sternal notch minus the distance between the lower edge of the carotid cuff and sternal notch. This value is entered into the computer and the Vicorder software computes the PWVcf.

Statistics

For the intra-rater reproducibility Bland-Altman plots were used.[13] Intraclass Correlation Coefficients (ICC) and Coefficients of Variation (CV) were calculated as well, as previously described by others.[14] The measurement results of the two devices were compared by Bland-Altman plots. In a Bland-Altman plot the differences between two measurements per patient are plotted against the means of two measurements per patient. If differences are associated with mean values, a correction has to be applied. The 95% Confidence Interval (95% CI) of the mean difference should include zero to exclude systematic differences. The Limits of Agreement (LoA) (± two times the Standard Deviation of the differences per patient) indicate the range between successive measurements in a subject without real change. Only changes greater than the LoA can be interpreted as "real" change, not due to measurement error.

Paired t-tests were performed to compare the difference between the BP measurements preceding the first and second ViCorder PWV measurement with the difference between the BP measurements preceding the first and second Sphygmocor PWV measurement to detect a possible difference in BP, since the ViCorder measurements were separated by a longer time interval than the Sphygmocor measurements.

All analyses were performed using SPSS 16.0. P-values smaller than 0.05 were considered statistically significant.

Results

Of the 40 invited subjects 38 were willing to participate. Two female subjects did not participate for practical reasons not related to the study. Useful results of repeated measurements were obtained in a total of 30 subjects. In three subjects the PWVcf values obtained by the SphygmoCor were rejected because of quality control reasons as described elsewhere.[10] One or both Vicorder recordings were missing in five patients for various reasons, mainly because they were not saved properly. Apart from this, the Vicorder was easy to use; the neck pad did not cause discomfort in the participants.

Table 1 summarizes the characteristics of these 30 subjects. The baseline characteristics of the eight patients without usable PWV measurements did not differ significantly from the entire group.

Table 1. Demographic characteristics of the study group (n=30).
Expressed as n and %. [§] Systolic BP > 140 (and/or diastolic BP>90 mmHg). No patients were using antihypertensive drugs. BP blood pressure.

Characteristics	Mean	SD	Range
Male	16	53.3	
Age (years)	46.9	13.6	21-74
Weight (kg)	82.6	13.4	56-110
Height (cm)	178.7	8.4	165-200
BMI (kg/m^2)	25.8	3.2	21-31
Heart rate (bpm)	59.6	10.6	42-85
Systolic BP (mmHg)	124.5	14.3	94-157
Diastolic BP (mmHg)	74.9	8.7	61-99
Hypertensive[§] patients	4	13.3	

The mean difference [95% CI] between repeated measurements was 0.09 [-0.20 – 0.38] m/s and 0.24 [-0.55 – 1.03] m/s, for the SphygmoCor and Vicorder, respectively. This means that neither of these differences was statistically significant different from 0. The LoA were -1.53 – 1.71 m/s and -4.24 – 4.72 m/s, for the SphygmoCor and Vicorder, respectively (Figure 1a and Figure 1b). The ICC was 0.76 and 0.54 for the SphygmoCor and the Vicorder, respectively. The CV was 9% and 22% for the SphygmoCor and the Vicorder, respectively. The mean PWVcf measured by the Vicorder was 0.58 [-0.20 – 1.35] m/s higher than the PWVcf measured by the SphygmoCor, i.e. not statistically significant different. The LoA between the two instruments were -3.50 – 4.66 m/s (Figure 2).

The paired t-tests showed no statistically significant difference in BP preceding the first and second Vicorder measurement and preceding the first and second SphygmoCor measurement (mean differences [95% CI] were 2.3 [-2.5 – 5.1] mmHg and 0.5 [-3.9 – 5.0] mmHg, for systolic and diastolic BP differences, respectively).

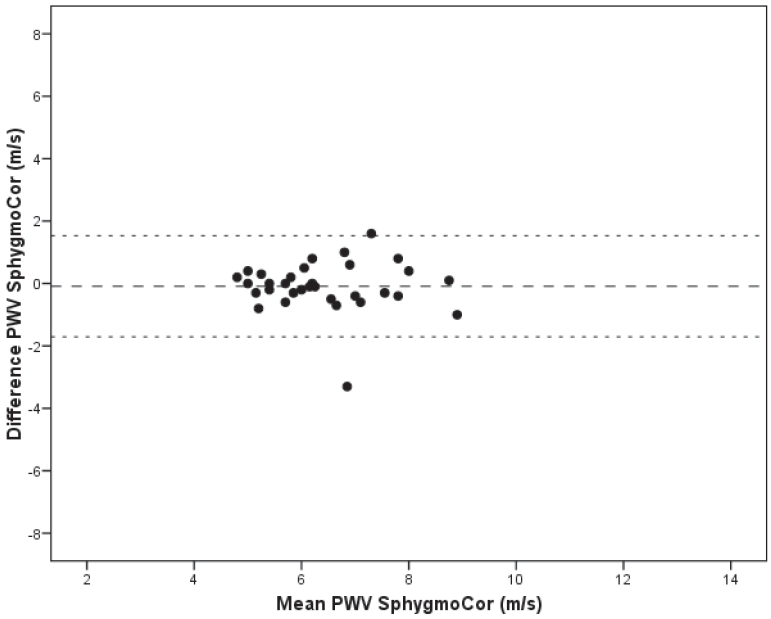

Figure 1a. Intra-rater reproducibility of pulse wave velocity (PWV) measurements by the SphygmoCor

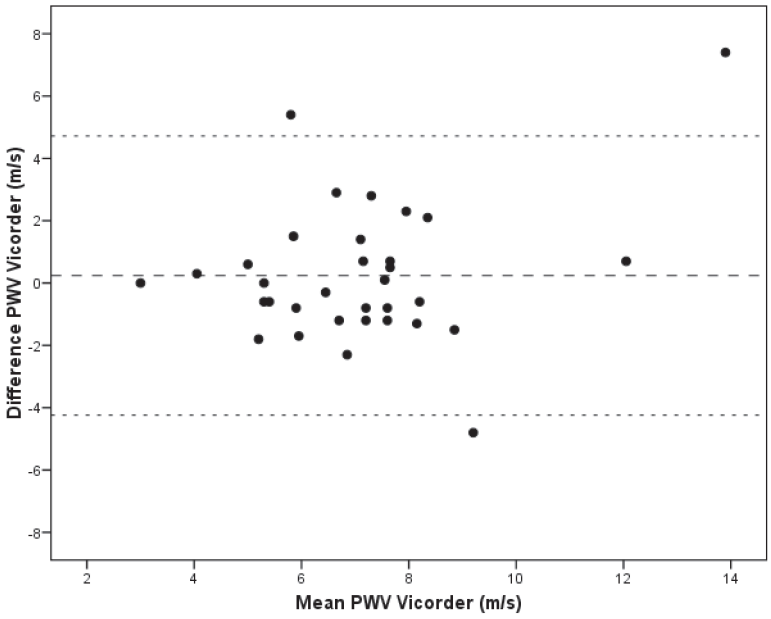

Figure 1b . Intra-rater reproducibility of pulse wave velocity (PWV) measurements by the Vicorder.

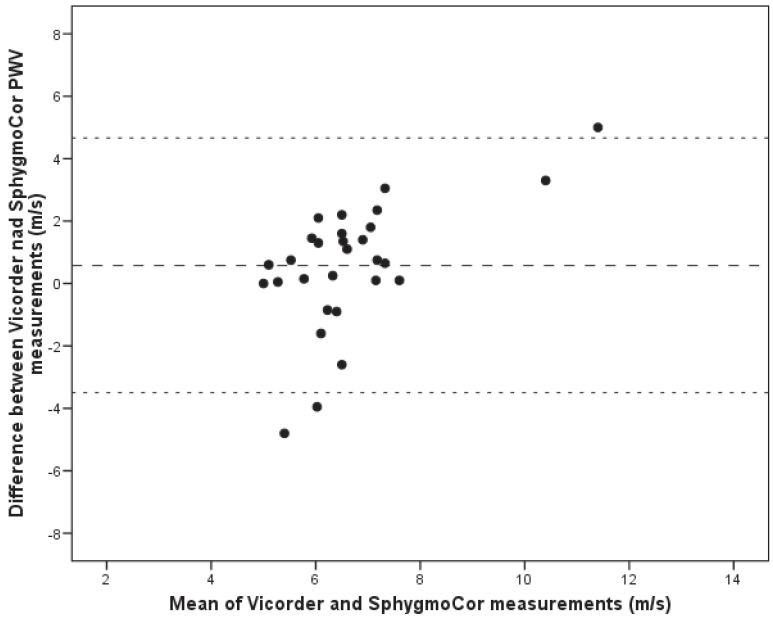

Figure 2. Comparison between pulse wave velocity (PWV) measurements by the Vicorder and SphygmoCor.

Discussion

The main finding of our study is that the LoA of both the SphygmoCor and the Vicorder exceed a value of 1.5 m/s. This indicates that changes in an individual less than 1.5 m/s cannot be determined reliably. Although there is no consensus about the size of a minimal clinically relevant difference, these LoA are larger than what we would consider clinically relevant. The LoA for the Vicorder were much wider than for the SphygmoCor, indicating that the reproducibility of the Vicorder is by far inferior.

The LoA we have found for the PWVcf measured by the SphygmoCor are smaller than those reported by Wilkinson (-2.27– 2.41 m/s) in a group of 10 healthy subjects, 8 hypertensive and 6 hypercholesterolemic patients.[11] The CV for the PWVcf measured by the SphygmoCor was in line with values found by others[15]: 13% vs. 9% in our study.

SphygmoCor uses the systolic upstroke to detect the pressure wave. Oscillometric devices (Vicorder) detect the time point of maximal pressure. The time point of maximal pressure during the pressure wave can differ from site to site. The systolic upstroke is amplified towards

the periphery. At peripheral measurement sites such as the brachial artery or the femoral artery the maximal pressure excursion will occur early in systole. In central arteries like the aorta and the carotid artery reflected pressure waves may cause the maximal pressure to occur late during systole. Pressure wave reflections vary from person to person and also from moment to moment. The fact that the maximal pressure occurs early during systole at the femoral artery, and at a later moment in the pressure cycle at the carotid artery, theoretically results in the calculation of a higher PWV. This is in agreement with our observation that we derived a PWV with Vicorder which was, on average, higher than the PWV calculated with SphygmoCor. The variability in the time point of maximal pressure excursions caused by variations in reflected pressures might in part explain the differences between PWV as calculated with both techniques. A technique which uses the systolic upstroke (SphygmoCor) is not hampered by variations in pressure later during the pressure cycle, and might thus be expected to show a better reproducibility. This is in agreement with our observations.

Another possible explanation for the observed differences between the Vicorder and SphygmoCor results could be the larger interval between the Vicorder measurements. The stiffness of elastic arteries measured by the PWV shows beat to beat differences due to beat to beat differences in blood pressure. However, the absolute differences are small.[16] We measured blood pressure before each PWV measurement and did not observe significant changes in blood pressure over time. Therefore we conclude that our results are not strongly influenced by the order of measurements.

The wide LoA values may be due to the cuff used at the carotid site. The pulse wave recorded at this site was frequently not accurate, with numerous artifacts being recorded, and irregular shapes of the pressure curve. These might have altered the PWVcf calculations by the Vicorder. We think this is the cause of the inaccurate measurements because the pulse waves recorded at the femoral site had in almost all cases the expected regular shape. Unlike the other cuffs used by the Vicorder, the carotid cuff is not inflatable all around the neck, but just for a few centimeters, to be applied over the right carotid artery. It is possible that this adaptation of the carotid cuff is the cause of the inaccurate measurements because only locally inflating the pad to 65 mmHg may not be enough to exclude other oscillating movements by veins, other

arteries than the carotid artery, muscles or air from the trachea. These artifacts are recorded by the cuff and transmitted to the software, giving rise to additional curves besides the carotid artery pulse wave. However, the Vicorder does not provide any information to the user on which of these oscillometric curves are used for calculation of the PWV-cf and which are recognized as artifacts and excluded. This information is provided by the SphygmoCor software which marks in red the curves which are inaccurate and have not been used for analysis.

We became aware of this flaw already at the beginning of the recordings and have tried several ways to reduce the amount of artifacts. We instructed the patients to lie absolutely still, to take a deep breath, exhale and hold their breath while the recordings were made; we tried positioning the head in such way that the neck muscles were completely relaxed, but unfortunately none of these adjustments improved the recordings.

The lack of experience or previous descriptions of the use of the Vicorder may have contributed to the results of the current study. However, we have followed the instructions in the Vicorder manual and those provided on site by a representative of the manufacturer (http://www.dopstudio.co.uk/VicorderManual.pdf). Furthermore, for five patients, one or two Vicorder recordings were not available, most because of faults in saving the data. The Vicorder software does not provide a warning when data are not saved properly by the investigator. However, these missing data probably did not alter the results of the study, because the available recordings of the remaining 33 subjects were consistent in showing multiple artifacts.

We conclude that the Vicorder, although it may be useful for many other applications, is unsuitable for accurate measurements of the PWVcf in adults and probably also in children. Before further research can be initiated with this device, we recommend the manufacturer to improve the neck pad and/or provide more detailed user information to solve the problems we encountered.

Acknowledgments

We are grateful to APC Cardiovascular Ltd Nederland for lending us the Vicorder device. We thank Danny van Maurik, neurophysiologic analyst for performing all measurements.

References

1. Laurent S, Cockcroft J, Van Bortel L*, et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-2605.
2. Blacher J, Guerin AP, Pannier B*, et al.* Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;99:2434-2439.
3. Groothoff JW, Gruppen MP, Offringa M*, et al.* Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. *Kidney Int* 2002;61:621-629.
4. Rajzer MW, Wojciechowska W, Klocek M*, et al.* Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. *J Hypertens* 2008;26:2001-2007.
5. Baulmann J, Schillings U, Rickert S*, et al.* A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. *J Hypertens* 2008;26:523-528.
6. McEniery CM, Yasmin, Hall IR*, et al.* Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46:1753-1760.
7. Cruickshank K, Riste L, Anderson SG*, et al.* Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085-2090.
8. Lehmann ED, Hopkins KD, Rawesh A*, et al.* Relation between number of cardiovascular risk factors/events and noninvasive Doppler ultrasound assessments of aortic compliance. *Hypertension* 1998;32:565-569.
9. Asmar R, Benetos A, Topouchian J*, et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995;26:485-490.
10. Frimodt-Moller M, Nielsen AH, Kamper AL*, et al.* Reproducibility of pulse-wave analysis and pulse-wave velocity determination in chronic kidney disease. *Nephrol Dial Transplant* 2008;23:594-600.
11. Wilkinson IB, Fuchs SA, Jansen IM*, et al.* Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998;16:2079-2084.
12. New Portable Device Aids in Detecting Peripheral Vascular Disease. *Journal of Clinical Engineering* 2008;33:65.
13. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310.

14. Papaioannou TG, Karatzis EN, Karatzi KN*, et al.* Hour-to-hour and week-to-week variability and reproducibility of wave reflection indices derived by aortic pulse wave analysis: implications for studies with repeated measurements. *J Hypertens* 2007;25:1678-1686.
15. Plantinga Y, Ghiadoni L, Magagna A*, et al.* Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. *Am J Hypertens* 2007;20:392-397.
16. Giannattasio C, Salvi P, Valbusa F*, et al.* Simultaneous measurement of beat-to-beat carotid diameter and pressure changes to assess arterial mechanical properties. *Hypertension* 2008;52:896-902.

5 Carotid artery disease in Hodgkin lymphoma survivors compared to healthy controls

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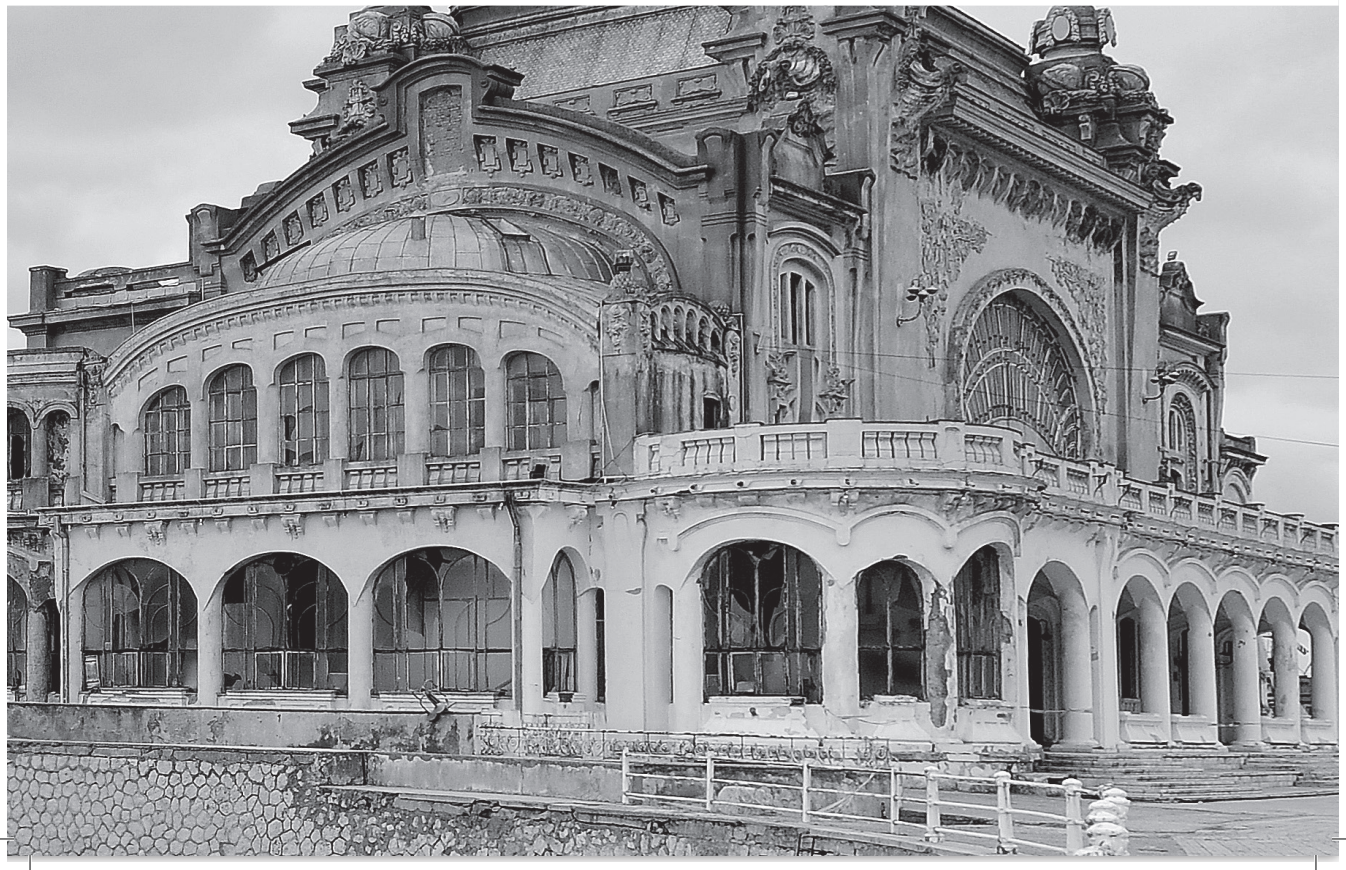

Abstract

Background

Hodgkin lymphoma survivors (HLS) are at increased risk of developing strokes and TIA's mostly long after treatment with radiotherapy. The purpose of this study is to investigate the prevalence of subclinical atherosclerosis assessed by intima-media thickness (IMT) and occurrence of plaque.

Methods and results

Eighty-two HLS and 40 age and gender matched control subjects underwent bilateral ultrasound investigations of subclavian, carotid and vertebral arteries. Plaque occurrence and stenosis were evaluated in these arteries. IMT was measured in the common carotid artery. Radiotherapy on the neck (20-44Gy) was included in the therapy regimen of 39 HLS. Mean IMT was higher in HLS treated with radiotherapy (0.595mm) versus HLS treated without radiotherapy (0.546mm, adjusted p=.000) and controls (0.550mm, adjusted p=.027). If irradiated HLS had a follow-up of 15 years or more from radiotherapy, their IMT was highest (0.631mm), after adjusting for traditional cardiovascular risk factors. IMT was positively associated with current age (p=.000), abdominal circumference (p=.037), pack years of smoking (p=.001), radiotherapy on the neck and follow-up time from diagnosis. Plaque was present in 46.2% of HLS treated with radiotherapy, significantly more frequent than in non-irradiated HLS (23.3%, p=.031) and versus controls (7.5%, p=.000). Plaque was positively associated with current age (p=.046), female gender (p=.010), radiotherapy and follow-up time from diagnosis. Nine irradiated HLS had a asymptomatic significant carotid artery stenosis versus three non-irradiated HLS and two controls.

Conclusions

Carotid artery disease is more prevalent among HLS treated with radiotherapy on the neck compared to non-irradiated HLS and healthy controls.

Introduction

Radiotherapy (RT) to the neck has often been associated with atherosclerosis and stroke in patients treated for head and neck cancer.[1-7] These patients were treated with high dose RT and often harbor additional risk factors for vascular disease like smoking, male gender, older age at diagnosis and hypercholesterolemia.[2] RT is presumed to accelerate the already existing atherosclerosis. In these patients, the risk for stroke increases 10 fold compared to the general population.[1]

Another group of patients frequently treated with RT to the neck are Hodgkin lymphoma patients. They are treated with lower dose RT, are on average younger at time of treatment and have less often other vascular risk factors. Nevertheless Hodgkin lymphoma survivors (HLS) also have a 2.2 and 3.1 fold increased risk of stroke and TIA respectively.[8] The etiology of these long-term complications in HLS is thought to be multifactorial, because HLS are often also treated with RT to the mediastinum and with chemotherapy. One large study in 2201 HLS showed that most cerebral ischemic events resulted from large artery atherosclerosis (36%) and cardioembolism (24%); the cause was unknown in 13%.[8]

Because long-term HLS have an increased risk of developing a wide scale [9] of therapy-related complications, efforts are being made to develop comprehensive screening programs for timely detection of these late sequelae. These screening programs mainly focus on the detection of secondary cancers, cardiovascular (CV) diseases and thyroid disorders.[10] Cerebrovascular complications have rarely been included in screening propositions. This is mainly due to the different causes and the low absolute excess risk of stroke and TIA.[8]

Intima media thickness (IMT) of the carotid artery is a strong predictor of stroke in high risk populations.[11] Furthermore it can be used together with the presence of plaque and other CV risk factors to stratify patients in high/low risk categories.[12] Subsequently high risk patients can be monitored more intensively and their risk factors can be treated accordingly.

Recently several studies reported on IMT measurements in HLS.[13-17] The results were inconsistent in demonstrating differences in IMT between HLS and controls. Furthermore it is hard to draw conclusions

due to combined results of HLS and survivors of other types of cancer and because patients were treated with different RT regimens. In the current study we present IMT measurements performed in adult HLS compared to a matched group of healthy controls. The purpose of this study is to investigate the prevalence of subclinical atherosclerosis assessed by IMT and plaque adjusted for patient- and therapy-related risk factors.

Methods

Between November 2007 and August 2008, 122 participants were enrolled in this study: 82 HLS and 40 age and gender matched control subjects. The control population consisted of randomly selected spouses of patients. At our institution all patients previously treated for HL are monitored at regular intervals by their hematologist to detect recurrences of HL or long-term complications of treatment. All HLS registered at our institution who were free of disease and had a follow-up from diagnosis of HL of more than 2 years were invited to participate in the current study (n=113). Nineteen HLS had died; the cause of death could be retrieved in 11 patients: seven suffered from a secondary malignancy, three from CV complications and one died from an infectious complication. Six HLS did not attend their regular check-ups and could not be traced. Another six HLS declined participation because of old age (n=3), long travelling distance (n=1) or without a specific reason (n=2). The patients who declined participation were slightly older than the included subjects (mean age 57 ±17 years) but did not differ in terms of treatment characteristics.

Patients were treated between 1969 and 2005 with different regimens. Typically extended field RT (mostly mantle field RT to the neck, mediastinum, axillary lymph nodes and sometimes para-aortic lymph nodes) was performed in patients with limited stage HL until the late 1990's, being replaced by involved field radiation in the more recently treated patients. (Figure 1) HLS with more advanced stages were primarily treated by chemotherapy (CT) to which RT was added in case of bulky disease, mostly located in the mediastinum. Recently CT and RT were combined in most patients (Figure 1). The radiation dose was 40Gy in fractions of 2 Gy when RT was the only treatment and mostly 30-36 Gy when RT was combined with CT.

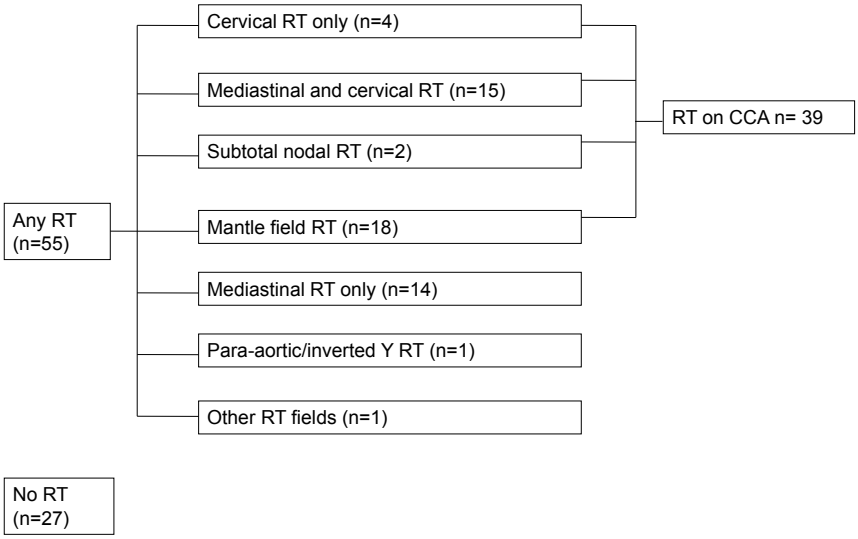

Figure 1. Treatment modalities in the 82 HLS.

Until the 1980's the CT consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were introduced as a part of the primary treatment.
Data was collected on the CV history and CV risk factors. Body mass index (BMI) and abdominal circumference were measured. Furthermore a blood sample was drawn after overnight fasting for determination of glucose, HbA1C and lipid profile.
IMT was assessed with the subjects in supine position, with the head tilted slightly to the contralateral side for the measurement in the common carotid artery (CCA). A 9-3 MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (Philips iU22 ultrasound system, Philips Inc.) was used to record the ultrasound images. The sonographer obtained longitudinal B-mode images of the left and right common CCA, immediately proximal to the carotid bifurcation, outside of a plaque, in case plaque was present in this predefined area. The sonographer adjusted focus and gained settings to optimise far-wall echoes and to minimise noise in the arterial lumen. Measurement of IMT was performed at the far wall of the CCA, in the 10mm segment proximal to the bifurcation, using the Philips QLAB IMT plug-in.

Ultrasound images were reviewed for plaque or stenosis in the common, bulb, internal and external segments of the carotid artery, as well as the subclavian and vertebral arteries on both sides and the innominate artery on the right side. Presence or absence of plaque deposits was recorded and the degree of stenosis was estimated from the peak systolic velocity measurements. A degree of stenosis of >50% was defined as being significant.
All measurements were done by one researcher in the same room, blinded for the initial treatment of the HLS. One neurologist (O.J.M.V) reviewed and approved the results, also blinded for the initial treatment of het HLS

Statistics

IMT

In order to analyze IMT, the total group of HLS was divided in patients in whom the radiation field included the common carotid artery (n=39 HLS) and patients in whom it did not include the common carotid artery (n=43 HLS) (Figure 1). IMT was measured in the right and left common carotid arteries, as eight patients had been treated with unilateral RT. IMT was thus compared between 3 groups: irradiated common carotid arteries of HLS (RT_{CCA}+, n=70), not irradiated common carotid arteries of HLS (RT_{CCA}−, n=94) and common carotid arteries of controls (controls, n=80). To account for this intra-individual variation, we used linear mixed models with a random intercept per patient when analyzing the IMT as an outcome variable.
In order to determine which parameters were predictors of IMT, models containing only one predictor were fitted for the entire group of HLS and control groups separately. First we examined traditional CV risk factors (age, male gender, cholesterol, glucose, blood pressure, smoking, abdominal circumference, BMI, current use of blood pressure or cholesterol lowering medication, family history of CV disease). Characteristics of HL treatment (age at diagnosis, follow-up since diagnosis, RT dose) were compared between HLS treated with and without RT. Variables with p-values <0.20 from the univariate analyses were included in the multivariate regression analyses.
We fitted a multiple linear mixed model for IMT including the following variables: RT_{CCA} (RT_{CCA} +/ RT_{CCA}−/controls), current age, gender, mean BP, current use of cholesterol lowering medication, HDL, LDL, pack years

of smoking, current use of blood pressure lowering medication. From the multiple regression model, adjusted mean IMT was estimated for the different RT_{CCA} groups, and those means were compared using the Bonferroni-adjusted post-hoc tests.

In the simple linear regression analysis, follow-up since HL (FU_{HL}) proved to be a variable associated with IMT; for obvious reasons, this variable cannot be defined for the control subjects. Since we were interested in the IMT values according to FU, we created a grouping variable combining RT_{CCA}+/ RT_{CCA}− and a dichotomized follow-up time since HL (FU_{HL}). This resulted in five groups: controls, patients with a longer follow-up than the cut-off period and RT_{CCA}+, patients with a longer follow-up than the cut-off period and RT_{CCA}-, patients with a shorter follow-up than the cut-off period and RT_{CCA}+, and patients with a shorter follow-up than the cut-off period and RT_{CCA}-. Choosing the cut-off point was performed by analyzing which FU_{HL} best predicted the IMT. We found that a FU_{HL} of 15 years predicted the IMT most accurately.

Finally, a second multiple linear mixed model was fitted for IMT. This model included the variables used in the first multiple linear model, except that the RT_{CCA}+/ RT_{CCA}−/controls grouping variable was replaced by the RT_{CCA+} and FU_{HL} grouping variable. From the multiple regression model, adjusted mean IMT was estimated for the different RT_{CCA}/follow-up groups, and those means were compared using the Bonferroni-adjusted post-hoc tests.

Plaque and stenosis

The occurrence of plaque was investigated in several cervical arteries and indicates the presence of atherosclerotic disease in a subject. The eight subjects treated with unilateral RT had either no plaque (n=6) or only plaque on the irradiated side (n=2). Therefore, we analyzed the occurrence of plaque for each individual, not for each artery. Thus, three groups were compared for the occurrence of plaque: HLS in whom the radiation field included the cervical arteries (RT_{neck}+, n=39), HLS in whom it did not include the cervical arteries (RT_{neck}-, n=43) and controls (controls, n=80). The comparison between these groups was performed using chi square tests (Figure 5). Similarly to the analysis of IMT, we used linear logistic regression to identify independent correlates of plaque.

Results

The baseline characteristics of the study population are described in Table 1.

Table 1. Baseline characteristics.

	Hodgkin Lymphoma survivors n=82		Control subjects n=40
	Radiotherapy on the CCA n= 39	No radiotherapy on the CCA n= 43	
Male (%)	51	58	55
Age (mean)	46.5	49	48
BMI (kg/m^2)	24.4	27.2	26.1
Abdominal circumference (cm)	92	99	96
Positive family history of CVD (%)	28	14	25
Smoking (pack years)	5.4	9.3	4.8
Glucose (mmol/l)	5.6	5.4	5.1
HbA1C (%)	5.7	5.6	5.5
HDL cholesterol (mmol/l)	1.53	1.41	1.41
LDL cholesterol (mmol/l)	3.08	3.04	3.19
Current use of cholesterol lowering medication (%)	36	9	5
Mean BP (mmHg)	96.7	100.3	95.4
Current use of BP lowering medication (%)	18	21	8
Age at diagnosis (mean) years	29.3	37.2	-
Time since diagnosis (mean) years	16.1	10.7	-
Treatment with anthracycline based CT (%)	48.6	76.6	-
Median radiotherapy dose (range) Gy	40 (20-44)	-	-

Using a simple linear mixed model, mean IMT (95% confidence interval (CI)) was significantly higher in the RT_{CCA}+ group 0.582mm (0.549-0.615mm) compared to the RT_{CCA}- group 0.538mm (0.498-0.580mm, p=.031) and versus controls 0.530mm (0.499-0.562mm, p=0.020).
After fitting a multiple linear mixed model, mean IMT was still significantly higher in the RT_{CCA}+ 0.595mm (0.570-0.620mm) compared to the RT_{CCA}- 0.546mm (0.520-0.572mm, p=.000) and versus controls 0.550mm (0.519-0.580mm, p=0.027) (Figure 2). In this model we adjusted for traditional CV risk factors which were predictors of IMT in univariable analysis (Table 2). Since RT_{CCA} and follow-up time since HL were treatment related factors associated with IMT (Table 3), we grouped HLS according to FU time since diagnosis. RT_{CCA}+ and FU_{HL}≥15

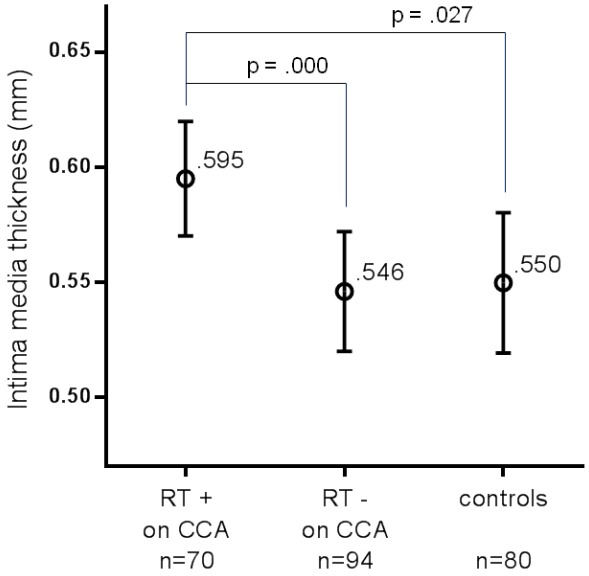

Figure 2. Adjusted means of IMT (95% CI) after fitting a mixed models linear regression including current age, gender, the RTCCA +/RTCCA-/control group, mean BP, current use of cholesterol lowering medication, HDL, LDL, pack years of smoking, current use of blood pressure lowering medication. Covariates appearing in the model are evaluated at the following values: current age = 47.6 years, mean BP = 95.8 mmHg, abdominal circumference = 95.6 cm, pack years of smoking = 6.6 years, HDL = 1.45 mmol/L, LDL = 3.1 mmol/L. All subgroups were compared with each other. Only statistically significant differences are shown in the figure.

was a significant predictor of IMT, together with current age, abdominal circumference and pack years of smoking (Table 4). The patients treated with RT_{CCA} more than 15 years before measurements had the highest IMT in multivariable analysis (Figure 3).

Plaques were found more frequently in HLS treated with RT compared to non-irradiated HLS (unadjusted p=.031) and to controls (unadjusted p=.000), (Figure 4). There was no significant difference in plaque occurrence between controls and HLS treated without RT on the neck (unadjusted p=.070, not illustrated in Figure 4). Moreover, HLS treated with RT on the neck more than 15 years ago had the highest prevalence of plaque (Figure 5).

Of all treatment related factors only RT on the cervical arteries and follow-up time since HL were significant predictor of plaque in HLS treated with RT. (Table 3) These factors, together with the traditional

Table 2. Univariable association of traditional risk factors with IMT and plaque in HLS and healthy controls. [a] Linear regression for the entire study group, n=244 common carotid arteries; [b] Logistic regression for the entire study group, n=122 subjects (HLS and controls). BP blood pressure, CI confidence interval.

	IMT			Plaque		
Risk factor	**Parameter Estimate**	**95% CI**	**p-value[a]**	**Odds ratio**	**95% CI**	**p-value[b]**
Current age,yrs	.005	.003 .006	.000	1.068	1.029 1.108	.001
Gender, male	.043	.008 .079	.017	0.413	0.179 0.954	.038
Mean BP, mmHg	.003	.001 .004	.000	1.031	0.998 1.065	.063
Blood pressure lowering medication	.112	.067 .157	.000	8.667	3.031 24.777	.000
HDL-c, mmol/l	-.046	-.091 -.002	.043	1.343	0.486 3.710	.570
LDL-c, mmol/l	.006	-.016 .027	.195	1.145	0.704 1.863	.585
Cholesterol lowering medication	.089	.046 .131	.000	7.594	2.898 19.896	.000
Smoking, cigarette pack years	.003	.002 .005	.000	1.025	0.995 1.056	.107
Abdominal circumference, cm	.003	.002 .005	.000	0.992	0.959 1.027	.647

Table 3. Univariable association of treatment related factors with IMT and plaque in HLS.
[a] Linear regression for the entire study group, n=244 common carotid arteries (CCA) ; [b] Logistic regression for the entire study group, n=122 subjects (HLS and controls). CI confidence interval.

Treatment related factor	Hodgkin lymphoma survivors					
IMT (mm)	**RT_{CCA}+**			**RT_{CCA}−**		
	Parameter Estimate	95% CI	p-value[a]	Parameter Estimate	95% CI	p-value[a]
Radiotherapy on the CCA	.044	.004 .083	.031	reference		
Follow-up since HL, yrs	.005	.003 .008	.000	-.001	-.006 .004	.648
Age at diagnosis, yrs	.002	-.001 .004	.226	.005	.003 .007	.000
Anthracycline containing chemotherapy	.057	-.047 .161	.269	.025	-.063 .114	.566
RT dose on the CCA (dose $_{>36Gy}$ vs. dose$_{<=36Gy}$)	.011	-.071 .049	.716			
Plaque	**RT_{neck}+**			**RT_{neck}−**		
	Odds ratio	95% CI	p-value[b]	Odds ratio	95% CI	p-value[b]
Radiotherapy on the neck	2.829	1.097 7.292	.031	reference		
Follow-up since HL, years	1.085	1.004 1.173	.039	1.023	0.928 1.128	.647
Age at diagnosis, years	1.032	0.978 1.163	.311	1.045	0.991 1.102	.102
Anthracycline containing chemotherapy	0.780	0.693 1.058	.210	1.500	0.448 5.018	.510
RT dose on the CCA (dose $_{>36Gy}$ vs. dose$_{<=36Gy}$)	1.570	0.565 4.360	.387	-		

Table 4. Multivariable association of factors related to IMT in the total study population n=244 common carotid arteries. * Model including current age, gender, the RT_{CCA} and FU_{HL} group, mean BP, current use of cholesterol lowering medication, HDL, LDL, pack years of smoking, current use of hypertension lowering medication, abdominal circumference.

Multiple mixed linear model with IMT as dependent variable*					
	Parameter estimate	95% CI		p value	F
Age	.003	.001	.004	.000	18.1
Abdominal circumference, cm	.001	.0001	.003	.037	4.5
Cigarette smoking, pack years	.002	.001	.003	.001	11.5
RT_{CCA} and FU_{HL} group					5.8
RT_{CCA}+ and FU_{HL}≥15	.087	.046	.129	.000	
RT_{CCA}+ and FU_{HL}<15	.009	-.030	.049	.649	
RT_{CCA}− and FU_{HL}≥15	-.006	-.046	.035	.787	
RT_{CCA}− and FU_{HL}<15	-.003	-.036	.030	.841	
controls	reference				

CV risk factors with p-values <0.20 in univariate analysis (Table 2) were used in a multivariable model (Table 5). In this model the RT_{neck}+ and FU_{HL}≥15 group had the highest odds for the occurrence of plaque when compared to controls (Table 5). HLS treated with RT less than 15 years before this study also had a significant higher odds ratio for the occurrence of plaque vs. controls, albeit slightly lower than the RT_{neck}+ and FU_{HL}≥15 group. (Table 5)

Significant arterial stenoses were present in 9 patients who were treated with RT. In these patients the following stenoses were encountered (more than one per patient possible): 5 subclavian stenoses (none with

Table 5. Multivariable association of factors related to plaque in the total study population n=82 subjects. * Model including current age, gender, the RT_{neck} and FU_{HL} group, mean BP, current use of cholesterol lowering medication, pack years of smoking, current use of hypertension lowering medication

Multivariable logistic regression model with Plaque (yes/no) as dependent variable*				
	Odds ratio	95% CI		p value
Age	1.062	1.001	1.126	.046
Male gender	0.225	0.072	0.701	.010
RT_{neck} and FU_{HL} group				.028
RT_{neck}+ and FU_{HL}≥15	14.842	2.757	79.909	.002
RT_{neck}+ and FU_{HL}<15	7.564	1.158	49.425	.035
RT_{neck}- and FU_{HL}≥15	2.155	0.255	18.225	.481
RT_{neck}- and FU_{HL}<15	3.957	0.720	21.758	.114
Controls	reference			

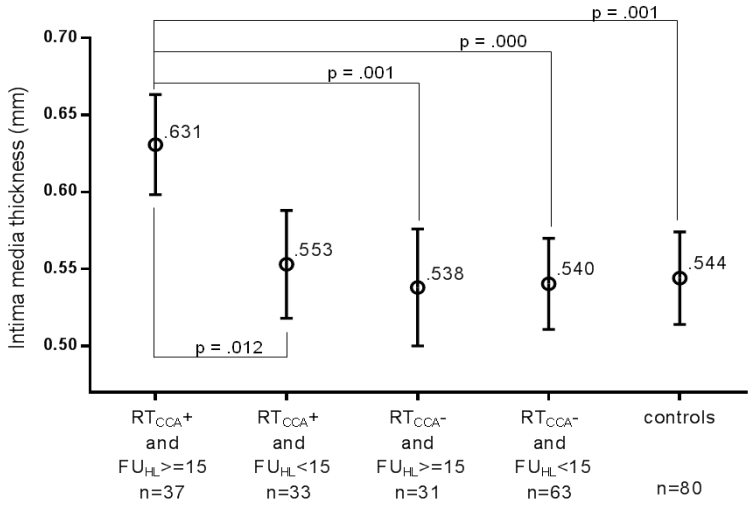

Figure 3. Adjusted means of IMT (95% CI) after fitting a mixed models linear regression including current age, gender, the RTCCA and FUHL group, mean BP, current use of cholesterol lowering medication, HDL, LDL, pack years of smoking, current use of blood pressure lowering medication. Covariates appearing in the model are evaluated at the following values: current age = 47.6 years, mean BP = 95.8 mmHg, abdominal circumference = 95.6 cm, pack years of smoking = 6.6 years, HDL = 1.45 mmol/L, LDL = 3.1 mmol/L. All subgroups were compared with each other. Only statistically significant differences are shown in the figure.

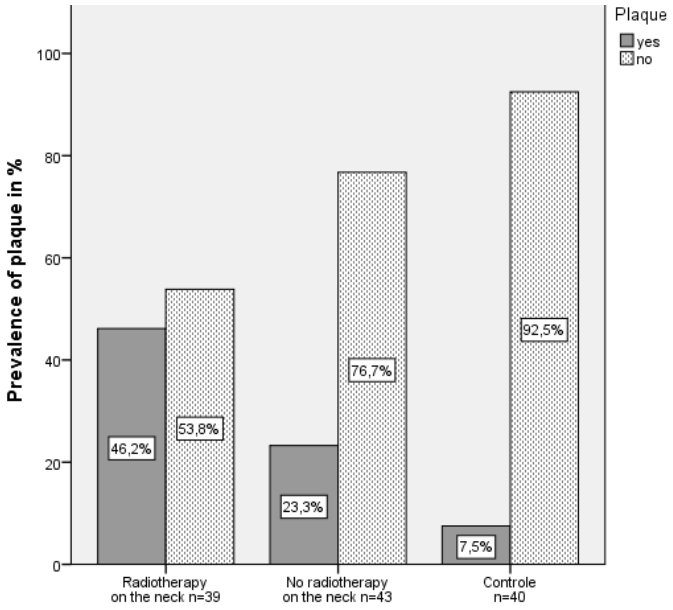

Figure 4. Prevalence of plaque.

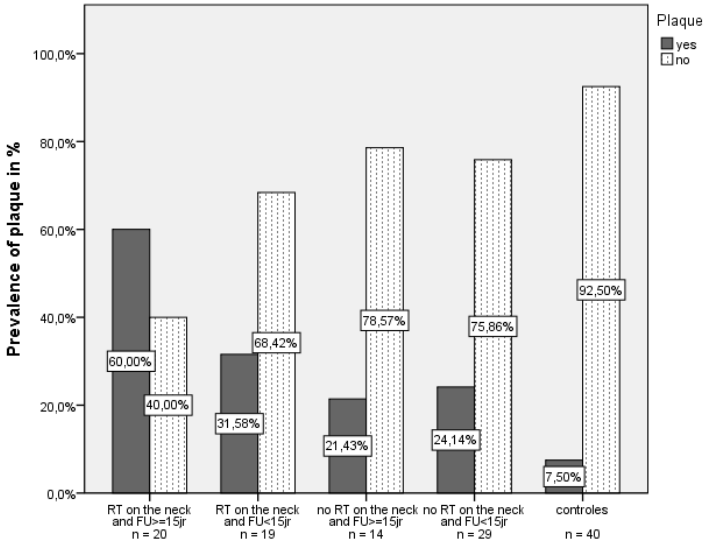

Figure 5. Prevalence of plaque according to the RT_{neck} and FU_{15yr} group.

a permanent steal), 5 stenoses in the external carotid artery (ECA), 3 in the vertebral artery, 2 in the internal carotid artery (ICA) and one the CCA (50-65% stenosis of the CCA). Three HLS treated without RT on the neck had significant stenoses: 3 in the ECA and one proximal subclavian stenosis. Two controls also had a significant stenosis, both in the ECA. None of the subjects were symptomatic (TIA or CVA) except one HLS treated with mantlefield RT who had a symptomatic stenosis of the ICA for which he received a stent, 5 years before this study, 22 years after RT.

Discussion

The present study demonstrates that IMT of the CCA is significantly increased in HLS treated with RT on the neck when compared to non-irradiated HLS and controls. The group treated with RT 15 years or longer ago had the highest IMT, whereas the patients irradiated less than 15 years ago had an IMT comparable with non-irradiated HLS and controls. Furthermore, all HLS treated with RT on the neck, regardless of follow-up time from RT, had higher odds of having atherosclerosis of the cervical arteries, demonstrated by the presence of plaque.

These findings are in concordance with earlier cohort studies demonstrating an increased risk of neuro- and cardiovascular disease more than 10 years after RT in HLS and other cancer survivors.[1, 8, 18-21] Since there is also evidence that RT accelerates atherosclerosis, age at treatment could be a significant predictor of IMT after RT as well. Hull et al. [21] identified 2 groups of patients at risk for cerebrovascular damage after RT. First, older patients with probable pre-existing vascular disease, in which RT apparently accelerated atherosclerosis. In this group with median age of 51 years, vascular disease developed a relatively short time interval after RT (median 5.6 years). Second, younger patients (median 20 years of age) had a longer latency period before diagnosis (median 20.8 years). In our study we would thus have expected patients treated with RT at older age to have increased IMT when compared to patients younger at RT with presumably atherosclerosis-naïve arteries. Yet, age at RT was not a predictor for IMT in our study. Probably, our study group was too young (mean age at treatment= 29.3 years) to find this difference. This finding is in concordance with an older study [22] in 118 mainly HLS, who did not find a greater sensitivity to radiation in older patients with presumed pre-existing atherosclerosis.

Our results showing an effect of follow-up time since RT on IMT are in concordance with earlier studies describing IMT after RT. Dorresteijn et al.[5] showed that IMT was significantly increased in the irradiated CCA compared to the non-irradiated side after RT in head and neck cancer patients. This difference was only found in patients with a post-RT interval of 10 years or longer. In a recent study in 30 pediatric cancer survivors, IMT was positively associated with years after treatment.[23] Moreover Gianicolo et al.[14] showed no difference in IMT between irradiated patients and controls, when the patients had completed RT at a mean of 2.9 years before (range 1month-6 years). The only study previously performed in 42 HLS (aged 18-37 at screening) also shows a significantly greater IMT in irradiated patients versus 33 healthy controls (0.51 mm vs. 0.43 mm; $p < .005$). This study does not report on the relationship of the follow-up time and IMT, but all HLS had undergone neck RT > 5 years earlier (mean 13 years, range 5.1-22.8 years).[13]

Animal studies and human clinical pathological studies have consistently shown that radiation induces or accelerates atherosclerosis.[24-28] A recent study, describing irradiated arteries in head and neck cancer

and breast cancer patients, showed an increased intimal thickening, proteoglycan deposition and inflammatory cell infiltrates.[27] These pathological changes translate clinically into increased IMT. This study was performed in patients with a mean FU of 3-4 years after RT. There was a non-significant effect of time on intima:media ratio (IMR), leading to an increased IMR with increasing FU, but the numbers were too small for a detailed analysis.[27]

In our study only the RT_{CCA}+ and FU_{HL}≥15 group had a significant higher IMT when compared to controls, while all irradiated HLS had a higher odds of plaque occurrence. As intima medial thickening is thought to be the first step in atherosclerosis, after which evident plaque formation occurs, one would expect the opposite of these findings: higher IMT in all irradiated HLS and more prevalent plaque only in the RT_{neck}+ and FU_{HL}≥15 group. This can be explained by the fact that the IMT is measured on a predefined location, outside of a plaque, on which location the IMT may be lower due to a lack of damage on that site. Plaque occurrence was not subject to this kind of 'sampling error', as we looked for plaque at various segments of the cervical arteries. Furthermore, in large populations the additive value of plaque to traditional risk factors for predicting CV disease, was higher than the addition of IMT, especially in women, while adding both plaque and IMT to the model resulted in the best area under the curve.[12] In a recent study carotid plaque burden was also found to correlate stronger with coronary artery calcium score than did IMT. [29]

Cigarette smoking and abdominal circumference were of influence on IMT on multivariable analysis, making it very important to address these issues during FU of HLS by their hematologist.[30] Female gender was an independent risk factor for the development of plaque, but was not a predictor of IMT. Just the opposite was observed: in univariate analysis, male gender was associated with a higher IMT. This is an interesting finding, which cannot be explained easily. It has been shown that female survivors of pediatric cancer have a higher risk of developing long-term RT related complications like CV disease [31] , hypothyroidism and cognitive dysfunction.[32] The occurrence of plaque for which female HLS are at increased risk in our study is an evident manifestation of atherosclerotic disease. IMT is not clearly increased in females, because of lower baseline IMT compared to males (resulting from the univariate analysis), which is a known phenomenon from the general

population.[33] The measurements of IMT are arbitrarily performed on a segment of the CCA where there might be no or limited vascular damage, but the presence of plaque clearly indicates atherosclerosis. Therefore we believe that the association of female gender and the presence of plaque is indicative of the fact that female HLS are at higher risk of developing atherosclerosis after RT. This finding can be due to the fact that female HLS develop premature menopause due to gonadotoxic chemotherapy, which was shown earlier to be associated with an increased risk of CVA.[34] As previously discussed by others, the underlying mechanism remains unknown.[23]

In our population CT regimens included anthracyclines in 80% of the HLS treated by CT. HLS treated with CT only did not show a significantly higher IMT nor had more frequently plaque than controls. This is in accordance with another study in HLS in which CT did not increase the risk of CVA and TIA.[8]

A recent study by de Bruin et. al [8] pointed out that the risk of CVA and TIA is increased in HLS, but that screening by carotid ultrasound is not recommended due to the small excess number of events and other probable causes of CVA and TIA like CV disease. In our study population only one patient had a carotid artery stent due to symptomatic stenosis. All other 12 HLS diagnosed with significant stenoses in our study were asymptomatic and, according to current guidelines, are not eligible for surgical or endovascular treatment of the stenoses in order to prevent the occurrence of TIA or CVA. Although the asymptomatic stenoses will not be treated endovascularly, it is important to recognize these stenoses in HLS in order to instruct these patients to be alert of symptoms of TIA or CVA and to further modify their CV risk factors. Further, large longitudinal studies are needed to follow-up the HLS and identify the most important risk factors for CV disease: IMT, plaque, stenoses or other factors. Only than prediction models can be built which incorporate traditional risk factors and other treatment-associated risk factors in HLS and decisions can be made for the initiation of medical therapy (cholesterol or blood pressure lowering for example) or closer follow up. The cohort of HLS described in this study will be followed in order to determine whether IMT or plaque better predict the occurrence of symptomatic CVA, TIA or other cardiovascular end-points.

Our study is limited by its cross-sectional design, as patients had different FU periods. This disadvantage yields an advantage; it enabled us to determine the effect of time post-RT on the IMT. A major limitation is the fact that in time RT techniques have changed making it impossible to determine if FU time or the older techniques are the cause of the found differences. Over the years the radiation fields have become less extensive, and RT intensity has decreased. In our study most patients were treated with 40 Gy in total and only 13 had received 36 Gy or less (one patient treated with 20 Gy), mostly in recent years. These small differences and small numbers make it impossible to determine the role of the older techniques. Further studies in HLS treated in the modern time should clear out whether these patients are still at risk of carotid artery disease when treated with lower doses RT.

In conclusion RT seems to induce intima media thickening and the formation of atherosclerotic plaque which become more evident with longer follow-up of more than 15 years. Further studies are needed to establish the risks associated with newer RT techniques and to establish the benefits of screening for and treatment of CV risk factors in HLS.

References

1. Dorresteijn LD, Kappelle AC, Boogerd W*, et al.* Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol* 2002;20:282-288.
2. So NM, Lam WW, Chook P*, et al.* Carotid intima-media thickness in patients with head and neck irradiation for the treatment of nasopharyngeal carcinoma. *Clin Radiol* 2002;57:600-603.
3. Smith GL, Smith BD, Buchholz TA*, et al.* Cerebrovascular disease risk in older head and neck cancer patients after radiotherapy. *J Clin Oncol* 2008;26:5119-5125.
4. Haynes JC, Machtay M, Weber RS*, et al.* Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 2002;112:1883-1887.
5. Dorresteijn LD, Kappelle AC, Scholz NM*, et al.* Increased carotid wall thickening after radiotherapy on the neck. *Eur J Cancer* 2005;41:1026-1030.
6. Cheng SW, Wu LL, Ting AC*, et al.* Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999;178:323-328.
7. Brown PD, Foote RL, McLaughlin MP*, et al.* A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2005;63:1361-1367.
8. De Bruin ML, Dorresteijn LD, van't Veer MB*, et al.* Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst* 2009;101:928-937.
9. van Leeuwen-Segarceanu EM, Dorresteijn LD, Pillen S*, et al.* Progressive muscle atrophy and weakness after treatment by mantle field radiotherapy in Hodgkin lymphoma survivors. *Int J Radiat Oncol Biol Phys* 2012;82:612-618.
10. Ng A, Constine LS, Advani R*, et al.* ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer* 2010;34:211-227.
11. Lorenz MW, Markus HS, Bots ML*, et al.* Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007;115:459-467.
12. Nambi V, Chambless L, Folsom AR*, et al.* Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010;55:1600-1607.
13. King LJ, Hasnain SN, Webb JA*, et al.* Asymptomatic carotid arterial disease in young patients following neck radiation therapy for Hodgkin lymphoma. *Radiology* 1999;213:167-172.

14. Gianicolo ME, Gianicolo EA, Tramacere F*, et al.* Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. *Cardiovasc Ultrasound* 2010;8:8.
15. Martin JD, Buckley AR, Graeb D*, et al.* Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. *Int J Radiat Oncol Biol Phys* 2005;63:1197-1205.
16. Bilora F, Pietrogrande F, Campagnolo E*, et al.* Are Hodgkin and non-Hodgkin patients at a greater risk of atherosclerosis? A follow-up of 3 years. *Eur J Cancer Care (Engl)* 2010;19:417-419.
17. Bilora F, Pietrogrande F, Petrobelli F*, et al.* Is radiation a risk factor for atherosclerosis? An echo-color Doppler study on Hodgkin and non-Hodgkin patients. *Tumori* 2006;92:295-298.
18. 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;22:3139-3148.
19. Aleman BM, van den Belt-Dusebout AW, Klokman WJ*, et al.* Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003;21:3431-3439.
20. Bowers DC, McNeil DE, Liu Y*, et al.* Stroke as a late treatment effect of Hodgkin's Disease: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2005;23:6508-6515.
21. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
22. Elerding SC, Fernandez RN, Grotta JC*, et al.* Carotid artery disease following external cervical irradiation. *Ann Surg* 1981;194:609-615.
23. Meeske KA, Siegel SE, Gilsanz V*, et al.* Premature carotid artery disease in pediatric cancer survivors treated with neck irradiation. *Pediatr Blood Cancer* 2009;53:615-621.
24. Brosius FC, 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981;70:519-530.
25. Hoving S, Heeneman S, Gijbels MJ*, et al.* Single-dose and fractionated irradiation promote initiation and progression of atherosclerosis and induce an inflammatory plaque phenotype in ApoE(-/-) mice. *Int J Radiat Oncol Biol Phys* 2008;71:848-857.
26. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. *Catheter Cardiovasc Interv* 2008;72:563-568.
27. Russell NS, Hoving S, Heeneman S*, et al.* Novel insights into pathological changes in muscular arteries of radiotherapy patients. *Radiother Oncol* 2009;92:477-483.

28. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum Pathol* 1996;27:766-773.
29. Sillesen H, Muntendam P, Adourian A*, et al.* Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. *JACC Cardiovasc Imaging* 2012;5:681-689.
30. van Leeuwen-Segarceanu EM, Bos WJ, Dorresteijn LD*, et al.* Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. *Cancer Treat Rev* 2011;37:391-403.
31. Lipshultz SE, Lipsitz SR, Mone SM*, et al.* Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995;332:1738-1743.
32. Armstrong GT, Sklar CA, Hudson MM*, et al.* Long-term health status among survivors of childhood cancer: does sex matter? *J Clin Oncol* 2007;25:4477-4489.
33. Juonala M, Kahonen M, Laitinen T*, et al.* Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: the cardiovascular risk in Young Finns Study. *Eur Heart J* 2008;29:1198-1206.
34. de Lecinana MA, Egido JA, Fernandez C*, et al.* Risk of ischemic stroke and lifetime estrogen exposure. *Neurology* 2007;68:33-38.

6 Coronary artery calcium score is increased after radiotherapy in Hodgkin lymphoma survivors

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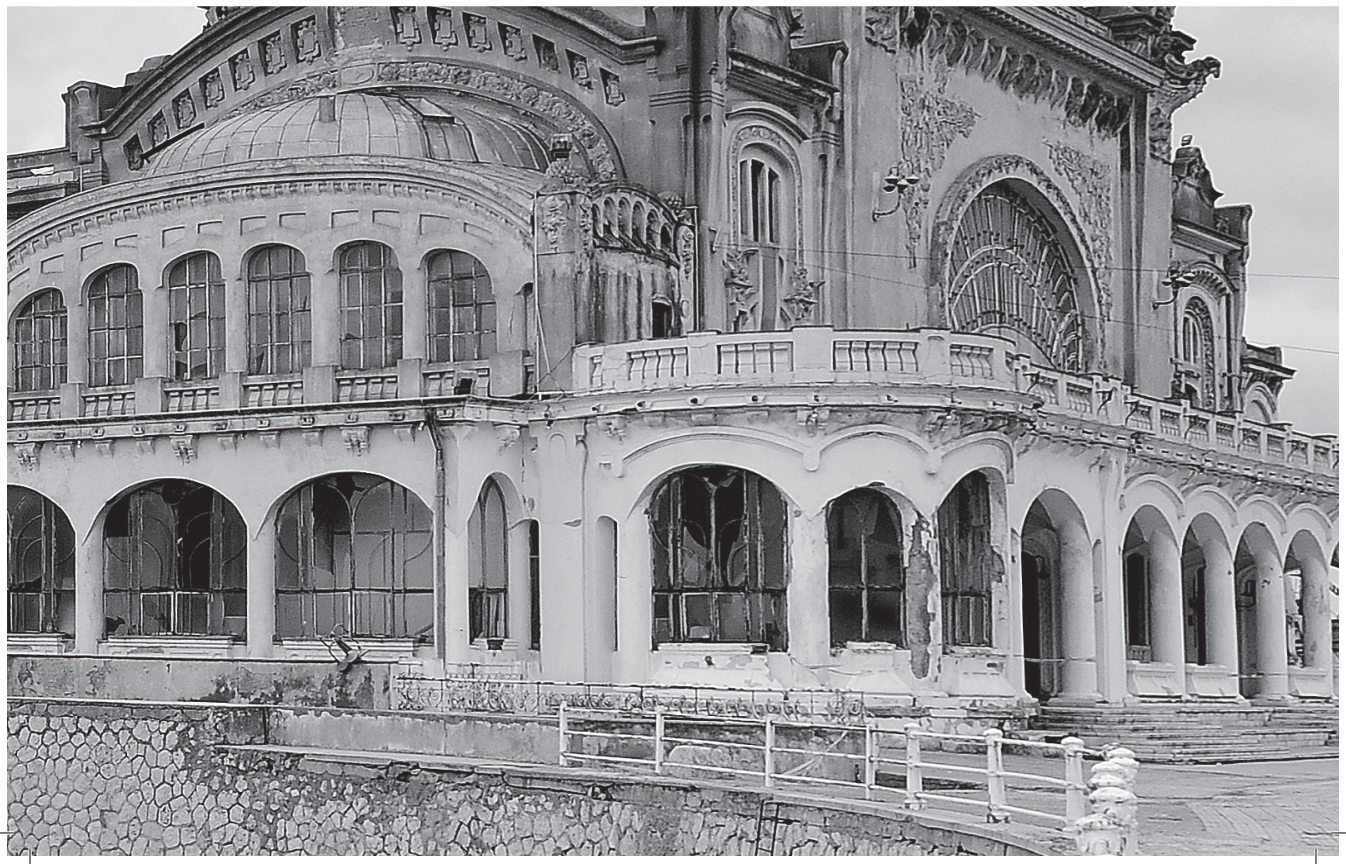

Abstract

Coronary artery disease (CAD) is a well know complication of mediastinal radiotherapy (MRT). Long term survivors of Hodgkin Lymphoma have an increased risk of myocardial infarction compared to the general population. Pre-clinical CAD, detected using modern imaging techniques, has been rarely described in these patients. In this cross-sectional study we describe 82 Hodgkin Lymphoma survivors (HLS) with a mean current age of 47.8 years and mean follow-up time from diagnosis of 13.4 years. Fifty patients were treated with MRT with or without chemotherapy. Seventy-five patients underwent coronary artery calcium (CAC) score measurements. Five HLS treated with MRT and one treated without MRT had already developed symptomatic CAD before screening. During four years follow-up after screening, two more patients developed CAD for which revascularisation therapy was needed. Significantly increased CAC-scores (i.e. CAC-score > 75th percentile for age and gender) were more frequently observed in HLS treated with MRT 41.3%, than in HLS treated without MRT 10.3% (p=.004). In multivariable analysis, HLS treated with MRT ≥ 10 years ago had an odds ratio of 12.1 of having a CAC-score > 75th percentile compared to HLS treated without MRT. HLS irradiated < 10 years ago had a similar incidence of significantly increased CAC-scores compared to the no-MRT group. HLS treated with MRT and CAC-score > 75th percentile had more traditional cardiovascular risk factors (median 3) than HLS treated with MRT with a CAC-score < 75th percentile (median 2), p=.036. We therefore recommend that screening HLS by CAC-score measurements should begin 10 years after MRT and that traditional cardiovascular risk factors should be addressed in this high risk population.

Introduction

Hodgkin Lymphoma survivors (HLS) have an increased risk to develop coronary artery disease (CAD). The risk remains increased for at least 25 years following treatment [1] and is mainly associated with mediastinal radiotherapy (MRT).[1-3] The overall 30-year cumulative incidence of myocardial infarction was 12.9% in 1241 mediastinally irradiated patients[1] and recent screening studies showed an incidence of 11-16% of asymptomatic CAD in HLS treated with MRT.[4-6]

HLS suffering from CAD show less often typical angina pectoris than "regular" patients with CAD[7]. Irradiated patients often present with myocardial infarction or sudden cardiac death.[7-9] This suggests that patients with RT-induced CAD remain asymptomatic for a longer time, probably due to RT-related nerve impairment or reduced exercise tolerance.[10]

Screening programmes have been advocated for timely identification of CAD in asymptomatic HLS. The best screening method is however a matter of debate since the gold standard, coronary angiography is an invasive method, and not free of risk. The presence of coronary artery calcifications (CAC) was shown to have good diagnostic characteristics for the detection of significant coronary artery stenosis in the general population.[11] Asymptomatic subjects with a CAC-score of zero had no cardiac events during a follow-up period of three years. Furthermore, a CAC-score above the 75th percentile for age and gender had a positive predictive value of 45% for MI or cardiac death within 40 months.[11]

The aim of this study is to compare computer tomography (CT) detected CAC-scores in HLS treated with and without MRT. Furthermore we tried to identify risk factors (RFs) predisposing HLS to develop coronary artery calcifications.

Methods and patients

Participants

Between November 2007 and August 2008, 82 HLS underwent a screening program aimed at identifying complications of RT and chemotherapy. The study was approved by the institutional review committee. All subjects gave informed consent. All HLS registered at our institution who were free of lymphoma and had a follow-up from

diagnosis of HL of more than 2 years were invited to participate in the current study (n=113). Eighty-two HLS gave informed consent for participation in the current study. Nineteen HLS had died, six were lost to follow-up and six patients declined participation. Of these thirty-one not included patients, seven were diagnosed with CAD at a median of 18 years after MRT (six HLS had deceased before this study and one HLS was lost to follow-up). In the studied group, MRT was a part of the treatment regimen in 50 HLS. Sixty-six HLS were treated with chemotherapy which contained anthracyclines in 80% of the cases. Detailed treatment characteristics of the HLS were described in detail previously.[12]

Data was collected on the cardiovascular (CV) history and CV RFs. Blood pressure (BP), body mass index (BMI) and abdominal circumference were measured. A blood sample was drawn after overnight fasting to determine glucose, HbA1C and lipid profile. Hypertension was defined as a systolic BP >140 or diastolic BP > 90 or current use of BP lowering medication. Hypercholesterolemia was defined as a LDL cholesterol > 3.0 mmol/l, HDL cholesterol < 1.0 mmol/l or total cholesterol > 5.0 mmol/l or current use of cholesterol lowering medication. Overweight was defined as a BMI > 25kg/m^2. Older charts of patients with documented CAD before this screening study were evaluated in order to score the presence of RFs at diagnosis of CAD.

Of 82 HLS included in the study, 75 underwent a CAC-score measurement. Seven HLS did not undergo these screening studies: three patients died between the start of the screening study and the CT scanning and four withdrew informed consent (IC). The patients who died were all treated with MRT: two died of secondary malignancy after RT and one of heart failure due to constrictive pericarditis. Of the four patients who withdrew IC (one because of recently diagnosis of a malignancy and three without reason), three were treated without MRT. Only one patient who did not undergo CAC measurements had a history of CAD: coronary artery bypass graft (CABG) 11 years after HL. This patient was not treated with MRT and had 3 traditional RFs for CAD. These seven patients who did not undergo CAC-score measurements are described in the baseline table only.

CAC-score measurements were performed with a Philips 16 slice CT scanner (Philips Medical Systems, Best, the Netherlands).

A nonenhanced scan to calculate the total CCS was performed with the following scanning parameters: prospective ECG triggering, at inspiration, 2,5mm slice thickness, 120kV tube voltage, 55mAs tube current. Agatston scores were computed with the Extended Brilliance Workspace software (Philips Medical Systems, Best, the Netherlands).
Four years after the initial screening study a chart review was performed of the 82 HLS. Death, cause of death, symptomatic CAD and revascularisation interventions were scored.

Statistics

Statistical analyses were performed the after categorising patients in those with CAC-score > or < than the 75th percentile for age and sex, using the values from Schmermund et al. [13]
In order to identify those with a low risk of symptomatic CAD, analyses were also performed for HLS with CAC-scores ≥ 0. Comparisons between these groups were performed using chi square or independent students t-test. We used linear logistic regression to identify independent correlates of CAC-scores. Statistical analyses were performed with SPSS 18.0.

Results

Baseline characteristics of the study population are described in Table 1.

Median CAC-scores for the total group of HLS who underwent CAC-score screening was 0, since 43/75 HLS (52.4%) had a CAC score of 0, with an interquartile range of 102. Median CAC-score for HLS treated without MRT was 0, as 22/29 (75.9%) had a CAC score of 0, with an interquartile range of 4. For the HLS treated with MRT the median CAC was 4.7 with an interquartile range of 275.3.
A CAC-score > 75th percentile for age and gender was more frequently observed in HLS treated with MRT 41.3%, than in HLS treated without MRT 10.3% (p=.004). HLS irradiated less than 10 years ago did not show an increased incidence of CAC > 75th percentile compared to the no-MRT group (Figure 1). Furthermore, 65.7% of HLS treated with MRT longer than 10 years ago had a CAC-score > 0, compared to 24.1% of HLS treated without MRT (p=.001), Figure 2.

Tabel 1. Baseline characteristics

	Hodgkin Lymphoma survivors n=82	
	Radiotherapy on the mediastinum n= 50	No radiotherapy on the mediastinum n= 32
Male (%)	52	59
Current age (years)	47.6	48.1
BMI (kg/m^2)	24.7	27.7
Abdominal circumference (cm)	92.1	100.8
Positive family history of CVD (%)	30	16
Smoking (pack years)	4.6	11.9
Glucose (mmol/l)	5.5	5.4
HbA1C (%)	5.7	5.6
HDL cholesterol (mmol/l)	1.56	1.31
LDL cholesterol (mmol/l)	2.96	3.01
Current use of cholesterol lowering medication (%)	32.0	18.8
Mean BP (mmHg)	96.9	100.1
Current use of BP lowering medication (%)	22.0	15.6
Age at diagnosis (years)	30.0	38.8
Time since diagnosis (years)	16.5	8.1
Median RT dose on mediastinum (range) Gy	40 (28-44)	-
Anthracycline containing chemotherapy (%)	52	84

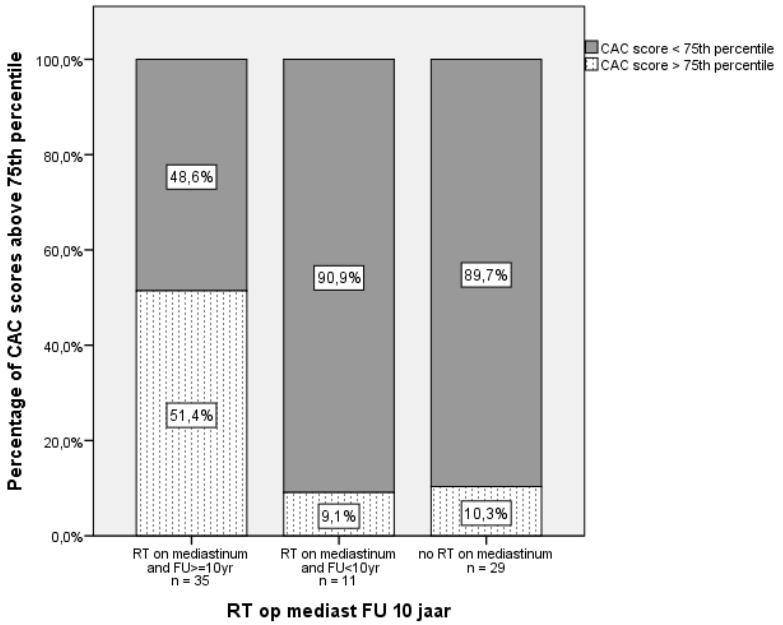

Figure 1. HLS with CAC score > 75th percentile for age and gender.

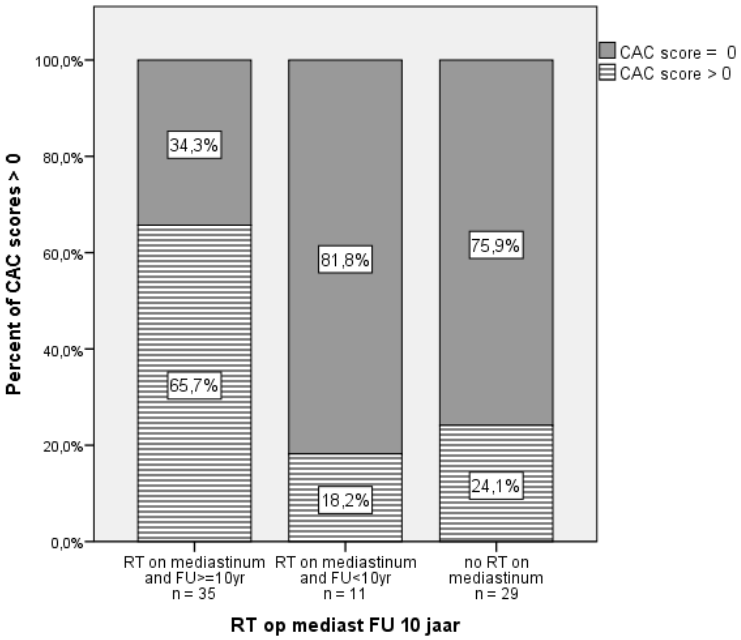

Figure 2. HLS with CAC score > 0.

Apparently HLS treated with MRT have the highest risk of developing CAD. Therefore, we looked for predictors of significantly increased CAC-score (i.e. > 75th percentile for age and gender) in the MRT group only. Within the group of patients treated with MRT patients with a CAC-score > 75th percentile had more traditional RFs (median 3) than HLS with a CAC-score < 75th percentile (median 2), p=.036 (Table 2). By comparison, all three HLS treated without MRT with a CAC-score > 75th percentile had four traditional CV RFs. HLS with CAC-scores > 75th percentile had more often hypercholesterolemia, were more frequently treated with blood pressure lowering medication and had more pack-years of smoking. Furthermore they had a longer follow-up time from MRT. There were no significant differences between MRT dose, use of anthracyclines or age at diagnosis (Table 2).

Significant parameters in the univariate analysis (Table 2) were used in order to determine significant predictors of a CAC-score > 75th percentile in a multivariate analysis. Since HLS treated more than 10 years ago had the highest prevalence of an abnormal CAC-score (Figure 1), we digotomised the follow-up time since MRT in ≥ 10 years and < 10

Table 2. Differences between HLS treated with MRT with CAC < or > 75th percentile.

	Hodgkin Lymphoma survivors treated with MRT		
	CAC score > 75th percentile n=19	CAC score < 75th percentile n=27	p- value
Male (%)	53	52	.958
Current age (years)	51.0	46.2	.207
Total CVD RF (mean / median)	2.4 / 3	1.6 / 2	.036
Positive family history of CVD (%)	26.3	37.0	.445
Hypercholesterolemia (%)	84.2	44.4	.007
Current use of chol. lowering med. (%)	31.6	22.2	.477
Hypertension %	31.6	18.5	.307
Mean BP (mmHg)	96.4	95.0	.692
Current use of BP lowering med. (%)	42.1	11.1	.032
Overweight (%)	36.8	37.0	.989
BMI (kg/m2)	23.8	25.7	.139
Abdominal circumference (cm)	93.4	92.0	.678
Smoking (%)	52.6	22.2	.033
Smoking (pack years) mean/median	8.2	2.5	.039
Time since diagnosis (years)	21.1	13.0	.003
Age at diagnosis (years)	28.3	32.2	.297
Dose MRT ≥ 40Gy (%)	84.2	70.4	.320
Anthracycline containing chemo. (%)	42.1	59.3	.251

Table 3. Multivariable association of factors related to CAC score > 75th percentile in the total studied group of 75 HLS.

Multivariable logistic regression model with CAC score >75th percentile as dependent variable			
	Odds ratio	95% CI	p value
MRT and FU group			.006
MRT and FU ≥10 yr	12.122	2.303 63.817	.003
MRT and FU <10 yr	1.476	.112 19.512	.767
No MRT	reference		
Current use of BP lowering med.	6.129	1.289 29.139	.023
Smoking	3.447	.818 14.517	.092
Dyslipidemia	2.891	.662 12.619	.158

years. In this multivariable analysis, HLS treated with MRT ≥ 10 years ago had an OR 12.1 (95% confidence interval 2.3-63.8) of having a CAC-score > 75th percentile compared to HLS treated without MRT (Table 3). Similar results were encountered in the multivariable analysis with CAC-score of > or =0 as a dependent variable (Table 4).

Table 5 describes patient- and treatment characteristics of HLS with abnormal CAC-scores. Seven HLS treated with MRT underwent revascularisation therapy: five before and two after CAC-score measurements. None had cardiovascular disease before MRT. Median interval between MRT and first revascularisation was 17 years. Median age when HLS needed revascularisation was 47 years. All HLS needing revascularisation were treated with 40 or 42 Gy. However, the mean FU from MRT of <40 Gy was lower, 8.27 years (n= 11 HLS with CAC-scores) compared to 18.8 years in the HLS treated with ≥40 Gy MRT (p=.000). No HLS with a CAC-score of 0 had been diagnosed with CAD or had undergone coronary revascularisation procedures

Table 4. Multivariable association of factors related to CAC score > 0 in the total studied group of 75 HLS.

Multivariable logistic regression model with CAC score > 0 as dependent variable				
	Odds ratio	95% CI		p value
MRT and FU group				.005
MRT and FU ≥10 yr	12.866	2.431	68.090	.003
MRT and FU <10 yr	1.329	.169	10.447	.787
No MRT	reference			
Dyslipidemia	8.217	2.135	31.625	.002
Smoking	6.731	1.429	31.709	.016
Current use of BP lowering med.	2.794	.519	15.053	.232

Tabel 5. Characteristics of patients with abnormal CAC scores. O-overweight/obesity of cholesterol lowering med), HT- hypertension (> 140/90 or current use of blood

Pat. Nr.	Sex	Current age	Follow-up from diagn.	Anthra-cyclin	Dose MRT	CAC-score	CAC >75th %
1	male	62	35	no	40	3100	yes
2	male	53	39	no	40	2920	yes
3	male	74	3	yes	0	2070	yes
4	female	50	21	no	40	1629	yes
5	male	60	27	no	40	1510	yes
6	male	61	15	yes	36	999	yes
7	female	79	13	no	40	869	yes
8	male	58	26	no	40	775	yes
9	male	46	28	yes	42	722	yes
10	male	60	37	no	44	414	yes
11	female	40	11	yes	40	300	yes
12	female	65	19	no	40	267	yes
13	female	65	3	yes	0	233	yes
14	female	56	14	yes	0	152	yes
15	male	37	16	yes	40	138	yes
16	female	61	10	yes	36	128	yes
17	male	48	23	no	40	79	yes
18	female	47	25	no	40	43,8	yes
19	female	45	19	yes	40	23	yes
20	female	31	11	yes	40	18	yes
21	female	33	15	no	40	9,5	yes
22	male	32	9	yes	36	8,2	yes
23	male	68	6	yes	28	391	no
24	male	60	4	no	0	160	no
25	male	55	2	yes	36	102	no
26	male	51	17	no	40	36,7	no
27	male	54	11	no	40	35	no
28	female	62	15	no	40	29	no
29	female	56	21	no	40	12,7	no
30	male	67	5	yes	0	7,9	no
31	male	41	15	yes	40	1,2	no
32	female	52	15	no	40	0,6	no

(BMI > 25), F-positive family history for CVD, HC-hypercholesterolemia (LDL> current use pressure lowering medication), S-ever smoking

Presenting signs of CAD	Revascularisation therapies	CV Risk factor
		HC, HT, MRT
AP	PCI LM 36yrs, CABG 37yrs after MRT	S, MRT
IP MI	PCI 1yr before HL	HC, HT, O, S
Atypical AP	PCI+re-PCI(stent thrombosis) RCA 17yrs after MRT	F, HC, O, MRT
AP	CABG LAD, RCA15yrs and PCI LAD 21yrs after MRT	HC, HT, S, MRT
		F, S, HC, O, MRT
		HC, HT, O, MRT
		HC, HT,S, MRT
screening MVR	CABG D1 30yrs after MRT, 2 years after CAC-score	MRT
		HC, HT, S, MRT
IP MI	CABG LAD, MO 3yrs; PCI LM, RCA 4yrs after MRT	F, HC, O, S, MRT
screening AVR	CABG LAD, RCA 17 yrs after MRT	HC, HT, S, MRT
		F, HT, O, S
		HC, HT, O, S
		HC, MRT
		HC, HT, O, S, MRT
		F, O, MRT
		HC, MRT
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		HC,HT, O
		HC, S, MRT
		HC, S, MRT
		HC, HT, O, S, MRT
		F, HC, MRT
		HC, O, S, MRT
		HC, S
anterior MI	PCI LAD 16 years after MRT, 1 year after CAC-score	HC, O, MRT
		FA, HC, O, S, MRT

Discussion

In this study we describe CAC-scores in HLS treated with and without RT to the mediastinum. Significantly increased CAC-score was more frequently present in HLS treated with MRT compared to not irradiated HLS. HLS treated with MRT ≥ 10 years ago had a 12.1 fold increased odds of having a CAC-score > 75th percentile compared to HLS treated without MRT. We defined a significant increased CAC-score as being > 75th percentile for age and gender since it was shown to be a better predictor of future cardiac events than the absolute score.[14] This is the first report comparing CAC-scores between adult HLS treated with and without MRT. Our findings are in accordance with large clinical epidemiological studies which did not show an increased risk of CAD in HLS treated with chemotherapy only.[1]

Furthermore, we show for the first time that only HLS treated with RT longer than 10 years ago have increased CAC-scores. HLS with CAC-scores > 75th percentile had a mean FU from MRT of 21.1 years versus 13.0 years in the HLS with CAC-scores <75th percentile. Studies published until now have found various data regarding the interval from MRT to the development of CAD. This is due to the differences in study populations (adult vs. paediatric populations, duration of follow-up from RT etc.) and the definition of the CAD endpoints (asymptomatic CAD vs. MI/AP vs. death from CAD). In most large cohort studies median FU period between RT and symptomatic CAD was 9–13 years.[7, 15-17] This is slightly lower than our findings, maybe due to the older treatment regimens and shorter FU time used in these older studies. In another study from the Netherlands with a similar follow-up duration from RT, Aleman et al. found a larger median interval until MI, of 19.5 years.[1] It was also observed that, the risk for MI significantly began to rise 10 years after MRT, in comparison to the general population.[1]

However, there are numerous descriptions of HLS who suffered from MI or even died from CAD within 10 years of MRT. [2, 5-6, 15, 17-19] Based on these findings Heidenreich et al. recommends to start screening for CAD 5 years after MRT.[5] When looking at our data, one HLS treated with MRT suffered from symptomatic CAD within 10 years after MRT (patient nr. 11). Starting screening for CAD at 5 years would not have identified this patient since she already developed a MI 3 years after MRT. This patient was probably already at risk of developing accelerated

CAD from MRT since she had 4 traditional RFs of CAD. Therefore, based on these small numbers we would recommend starting screening for CAD 10 years after MRT, this will probably result in the most efficient way of identifying HLS at risk.

Starting a screening programme only 10 years after MRT does not mean that treating physicians should not be aware of the cardiovascular RFs of HLS. We show, like other studies before [8-9, 16, 20], that HLS with more traditional RFs have higher odds of developing CAD. It is therefore important to consider these patients as having a high risk of developing cardiovascular disease and to address their RFs accordingly.[21] Chen et al. developed a decision-analytic model to evaluate lipid screening.[22] They demonstrated that lipid screening every 3 years would be the most cost-effective strategy. Furthermore, when statin therapy is initiated in screen-positive HLS, survival was shown to be improved.[22] There is no evidence to which cholesterol levels to aim, but a LDL-cholesterol of 2.6 mmol/L or lower is currently advised by experts, in accordance to guidelines for other high-risk populations.[23] The optimal screening interval for hypertension or diabetes mellitus has not been established. Different guidelines based on expert opinion recommend yearly measurements of blood pressure and fasting blood glucose.[21, 24] As we reviewed recently, various screening modalities have been evaluated to detect CAD in HLS.[25] Many of the studies described in this review did not use the gold standard, CAG, to confirm the significance of the abnormalities identified with non-invasive studies. Therefore, test characteristics are difficult to compare with each other and with the golden standard. In this study we chose for the CAC-score as a screening method for detecting CAD. This method has been used in two previous studies. Andersen et al. performed CAC-score measurements in 47 HLS treated with MRT. They observed fewer patients with a CAC-score of 0 (8/40 HLS compared to 21/41 HLS treated with MRT in our study) in a population with a longer FU time (22 vs. 16.5 years) and a slightly higher age (50 vs. 47.5 years). Further treatment and patient characteristics were similar in the two studies. This can implicate that CAD is a progressive process, in which even HLS without CAC will eventually progress to developing CAC in the future. Andersen et al. do not describe the effect of follow-up time from MRT on the CAC-score. This is probably due to the small variation within their studied

population, since all HLS were treated between 1980 and 1988. Based on their results the authors advocate that CAG should be seriously considered in HLS with CAC-scores > 200. A CAC-score < 200 should call for additional non-invasive testing.

In a pilot study Rademaker et al. present the results of CAC-score en CT-angiography in nine HLS. Eight patients had a CAC-score above the 75th percentile and one HLS had a CAC-score of 0. All eight HLS with a high CAC-score had CAD on CT-angiography: three had stenoses < 50%, two patients died soon and three patients underwent further investigations (one underwent an angioplasty, one a two vessel CABG and one a normal stress echocardiogram and underwent risk profile modification). This study also shows the potential of screening asymptomatic HLS by CAC-scores and CT-angiography, but also the need for performing additional stress testing to confirm clinically relevant CAD.

An important weakness of this study is the fact we did not systematically perform additional confirmation tests to evaluate the significance of CAD in HLS with high CAC-scores. However we followed the HLS 4 years after CAC-score measurements. One HLS (nr. 31) with a CAC 1.2 (CAC< 75th percentile) suffered from a large anterior MI 1 year after CAC measurement, after having AP complaints for some days but not attending a hospital. Another patient (nr. 9) was screened for CAD because of a planned mitral valve surgery. A significant asymptomatic stenosis of a diagonal branch was bypassed during valve replacement surgery. Furthermore one patient treated by mantle field RT 17 years before screening had died 2 years after CAC-score. At screening he had a CAC-score of 0, but two years later autopsy showed significant atherosclerosis of the right coronary artery. Another eight HLS have died during follow-up. None had undergone autopsy, but by reviewing the charts or based on information from the family physician, none were deceased because of CAD related causes. At four years follow-up, none of the13 living HLS with CAC-scores > 75th percentile without previous CAD had developed symptomatic CAD for which attending the hospital was needed.

The cross-sectional design of our study enabled us to determine the effect of time post-MRT on CAC-scores. However, in time RT techniques have changed, making it difficult to determine whether older techniques

are an important cause of the effects we observed. In our study most patients were treated with 40 Gy in total and only 11 had received 37 Gy or less, mostly in recent years. These small differences and small numbers make it impossible to distinguish the effects of radiation dose and radiation technique. A common limitation of studies analysing RFs of CAD is that we only measured cholesterol profiles and blood pressure at the time of the study. We were not able to estimate how long the HLS were exposed to specific RFs.

In this study we compared HLS (treated with and without MRT) indirectly to the general population described by Schmermund [13] since we categorized HLS as having CAC- scores higher or below the 75th percentile for age and gender. The CAC-score measurements from the study of Schmermund et al. were performed in a general population of asymptomatic patients referred by their primary care physician for CV risk stratification. Patients with an established history of CAD were excluded. After excluding the 6 HLS with proven CAD before this study, the percentage HLS treated with MRT more than 10 years ago with a CAC-score > 75th percentile was still higher (43.3%) than the expected 25% in the general population. Furthermore, the cohort described by Schmermund had a higher prevalence of cardiovascular risk factors (inherent to the reason for referral for CAC-score screening), underscoring once more the importance of recognising MRT as a risk factor for CAD. Comparing our cohort HLS with another recent study from the general population [26] shows that when looking at all different current age categories, HLS treated with MRT more than 10 years ago have a higher incidence of a CAC-score > 0. For the current age categories < 45 years, 45-54 years and 55-64 years the prevalence of a CAC score of 0 was 55.6% vs. 70%, 33.3% vs. 52% and 30% vs. 36% in HLS treated with MRT more than 10 years ago and the general population respectively. This shows that MRT induces calcification of the coronary arteries not only in older HL patients at treatment but also in young HL patients at MRT. Tota-Maharaj show in their study that subjects younger than 45 years at screening, with a CAC score > 400 (4% of subjects < 45years), have the worst 5 year survival of 85.8%. This is comparable with a person older than 75 years with a CAC-score of 400. These young subjects are thought to have a more aggressive form of atherosclerosis making them particularly vulnerable to a worse

outcome. We did not find any HLS currently younger than 45 years to have a CAC score > 400, maybe this is due to the fact that HL patients with CAD already present at MRT have died from CAD shortly after MRT, or due to the referral bias present in the article by Tota-Maharaj. We encountered however 5 HLS < 45 years treated with RT which have a CAC-score > 0. Atherosclerotic disease can be accelerated by MRT and develop into significant CAD.[27] This is best illustrated by patient nr. 13 with a high CAC score of 300 at screening who developed CAD shortly (3-4 years) after RT. These findings should encourage haematologists to further attempt patient tailored treatment in HL patients, incorporating CV risk screening at diagnosis of HL.

In conclusion, we show that HLS with ≥ 10 years follow-up from MRT are at increased risk of having significantly increased CAC-scores, compared to HLS treated without MRT. We therefore recommend that screening by CAC-score measurements should begin 10 years after MRT. In the meantime, haematologists should carefully monitor HLS for cardiovascular RFs. Patients should be encouraged to quit smoking; hypertension and hypercholesterolemia should be treated according to guidelines of patients at high risk of developing CAD. HLS with increased CAC-scores on screening should be referred for additional stress testing and be even considered candidates to undergo CAG. All HLS should be counselled on timely recognition of symptoms of CAD and timely attendance of medical assistance. Even HLS with a CAC-score of 0 should be warned about these signs, since a CAC-score of 0 does not rule out CAD. Evaluation of this screening recommendations and sequential follow-up after 10 years should be evaluated in prospective studies, especially in recently treated HLS. Future studies should reveal the importance of patient-tailored HL therapy, based not only on the HL risk factors but also on the CV risk profile.

References

1. Aleman BM, van den Belt-Dusebout AW, De Bruin ML*, et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878-1886.
2. 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;99:206-214.
3. Mulrooney DA, Yeazel MW, Kawashima T*, et al.* Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Bmj* 2009;339:b4606.
4. Andersen R, Wethal T, Gunther A*, et al.* Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. *Am J Cardiol* 2010;105:149-152.
5. Heidenreich PA, Schnittger I, Strauss HW*, et al.* Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol* 2007;25:43-49.
6. 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* 2009.
7. King V, Constine LS, Clark D*, et al.* Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1996;36:881-889.
8. Glanzmann C, Kaufmann P, Jenni R*, et al.* Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol* 1998;46:51-62.
9. Kleikamp G, Schnepper U, Korfer R. Coronary artery and aortic valve disease as a long-term sequel of mediastinal and thoracic irradiation. *Thorac Cardiovasc Surg* 1997;45:27-31.
10. 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;191:32-37.
11. Becker A, Leber A, Becker C*, et al.* Predictive value of coronary calcifications for future cardiac events in asymptomatic individuals. *Am Heart J* 2008;155:154-160.
12. van Leeuwen-Segarceanu EM, Dorresteijn LD, Vogels OJ*, et al.* Arterial stiffness is increased in Hodgkin lymphoma survivors treated with radiotherapy. *Leuk Lymphoma* 2012.
13. Schmermund A, Erbel R, Silber S. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. *Am J Cardiol* 2002;90:168-173.

14. Raggi P, Callister TQ, Cooil B*, et al.* Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000;101:850-855.
15. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol* 1993;11:1208-1215.
16. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
17. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ*, et al.* Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. *Radiother Oncol* 1999;51:35-42.
18. Pohjola-Sintonen S, Totterman KJ, Salmo M*, et al.* Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. *Cancer* 1987;60:31-37.
19. Brosius FC, 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981;70:519-530.
20. Myrehaug S, Pintilie M, Tsang R*, et al.* Cardiac morbidity following modern treatment for Hodgkin lymphoma: supra-additive cardiotoxicity of doxorubicin and radiation therapy. *Leuk Lymphoma* 2008;49:1486-1493.
21. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, 2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
22. Chen AB, Punglia RS, Kuntz KM*, et al.* Cost effectiveness and screening interval of lipid screening in Hodgkin's lymphoma survivors. *J Clin Oncol* 2009;27:5383-5389.
23. Overview of the approach to the adult survivor of classical Hodgkin lymphoma. http://www.uptodate.com.
24. Ng A, Constine LS, Advani R*, et al.* ACR Appropriateness Criteria: follow-up of Hodgkin's lymphoma. *Curr Probl Cancer* 2010;34:211-227.
25. van Leeuwen-Segarceanu EM, Bos WJ, Dorresteijn LD*, et al.* Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. *Cancer Treat Rev* 2011;37:391-403.
26. Tota-Maharaj R, Blaha MJ, McEvoy JW*, et al.* Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. *Eur Heart J* 2012;33:2955-2962.
27. Stewart FA, Heeneman S, Te Poele J*, et al.* Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649-658.

7 Assessment of valvular disorders in Hodgkin lymphoma survivors

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Manuscript in preparation

Abstract

Objective

The aim of this study is to identify risk factors for development of valvular heart disease in Hodgkin Lymphoma Survivors (HLS).

Background

As the number of cancer survivors grows because of advances in therapy, understanding long-term complications of these treatments becomes more important. In Hodgin Lymphoma, mediastinal radiotherapy (MRT) seems to cause valvular disease, and the prevalence might increase during follow-up.

Methods

In this cross-sectional study 82 HLS participated (52% male, mean age 47.8 years, 50 treated with MRT). Valvular heart disease was diagnosed by transthoracic echocardiography (TTE) and compared between HLS treated with and without MRT. Univariate and multivariate logistic regression analysis was used to identify predictors for valvular disease.

Results

During a median follow up of 13.4 years (range 2–39 years), severe valvular disease occurred in 24.5% of HLS with MRT compared to 3.4% of HLS without MRT(p=0.016). Irradiated patients had significantly more ≥mild aortic regurgitation (AR) (38.2% vs. 6.8%, p=0.007). Time after radiotherapy was an independent predictor for AR (OR 1.1, 95%CI 1.01–1.26, p=0.035). Within the MRT subgroup, time after radiation of >15 years was associated with AR (OR 4.70, 95%-CI 1.05-21.03, p=0.043), after adjusting for current age and hypertension. Valvular replacement was performed in 7 (14.0%) HLS with MRT compared to none in HLS without MRT.

Conclusion

The prevalence of valvular disease in HLS treated with MRT is high and increases with time following irradiation. Screening HLS for valvular disease by TTE might be worthwhile , starting 10 years after MRT.

Introduction

Of all cancers diagnosed in the developed world, Hodgkin Lymphoma (HL) accounts for approximately 0.6%, with about 8220 new cases and 1350 deaths due to HL in the United States annually.[1]

Treatment modalities for cancer have advanced over time, leading to an increase in the number of long-term cancer survivors. In HL, radiotherapy (RT) and chemotherapy used either alone, or in combination have led to significant improvement of disease-specific survival.[2]

Heart disease is a potential long-term adverse effect of mediastinal RT (MRT). Most frequently observed are valvular disease, pericarditis, coronary artery disease and cardiomyopathy, which might eventually lead to increased mortality.[3] Death of cardiac origin is estimated to be responsible for approximately one quarter of mortality in Hodgkin Lymphoma survivors (HLS) for other reasons than HL itself, which equals 2-5% of overall mortality in HL patients.[4-5]

There appears to be a strong association between the time following MRT and prevalence of cardiac disease, implicating that radiation-associated cardiovascular toxicity may be progressive.[2, 6] HLS, who are relatively young and survive for long periods, are therefore at increased risk of developing radiotherapy-induced heart disease.[6] However, the course of this disease is often asymptomatic and symptoms are often misinterpreted due to young age and lack of traditional cardiovascular risk factors.[7]

Most prevalent non-coronary cardiac disease are valvular disorders. Previous studies on this subject report differently on the occurrence of (preclinical) heart disease.[2, 6, 8-9] It remains challenging to identify which HLS are susceptible to develop radiation-associated valvular disorders.[2, 6] This study aims to assess the prevalence and clinical determinants of (asymptomatic) valvular disease in HLS who underwent MRT. Knowledge of these determinants is a prerequisite for the development of appropriate follow-up and screening programs in HLS.

Methods

Subjects

All disease-free HLS registered at our institution with a follow up of at least 2 years after the initial diagnosis, were invited to participate (n=113). Between November 2007 and August 2008, 82 HLS could be included. Nineteen HLS died, with a known cause of death in 11 patients (7 secondary malignancies, 3 cardiovascular complications, 1 infectious complication). Six patients could not be traced since they did not attend regular check-ups and another six declined participation (3 because of old age, one because of long travelling distance and 2 without specific reason). This study was approved by the institutional review committee. All participating subjects gave informed consent.

Treatment regimens

Patients were treated between 1969 and 2005 with different regimens. Until the late 1990's,typically extended field radiotherapy (mostly mantle field RT to neck, mediastinum, axillary lymph nodes and para-aortic lymph nodes) was performed in patients with limited stage HL, being replaced by involved field radiation in the more recently treated patients. HLS with more advanced stages of disease were primarily treated with chemotherapy (CT), to which radiotherapy was added in case of bulky disease, mostly located in the mediastinum. Until the 1980's, chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). Afterwards, anthracycline-containing regimens such as ABVD (doxorubin, bleomycin, vinblastine and dacarbazine) became part of the primary treatment.

Cardiac evaluation

Participants underwent cardiac evaluation by transthoracic echo-cardiography (TTE) to assess possible valvular disorders. Major risk factors for development of cardiac disease were recorded for each patient. History of cardiovascular disease (CVD), diabetes mellitus (DM) and hypercholesterolemia was noted, as well as family history of CVD, (current) use of medication and smoking behaviour. For each patient, blood pressure was measured and body mass index (BMI) was calculated. Lipid profile, glucose and NT pro-Brain natriuretic peptide (NT pro BNP) were determined after overnight fasting. All investigations

were conducted for the purpose of this study and took place between 2007 and 2009. Hypertension was defined as systolic blood pressure (BP) above 140 mmHg or diastolic BP below 90 mmHg at three different measuring points or current use of vasoactive medication. Dyslipidemia was defined as total cholesterol > 5.0 mmol/L/ or HDL cholesterol <1.0 mmol/L or LDL cholesterol > 3.0 mmol/L/ or triglycerides > 1.7 mmol/L.[10]

Echocardiography

Two-dimensional echocardiography, Doppler (color and continues wave) studies of aortic, mitral, tricuspid and pulmonary valves were obtained, using the Philips IE33 ultrasound scanner. Standard parasternal long-axis, short-axis, apical three, four and five-chambers and subcostal two-dimensional views were recorded.

The echocardiographic studies were interpreted by two independent experienced echocardiographers (J.B. and M.C.P), who were blinded to patient and treatment details. Valve regurgitation and stenosis were assessed using guidelines of the European Association of Echocardiography.[11-13] Symptomatic valvular disease that had already resulted in valvular replacements were graded according to severity at time of valvular surgery.

Statistical Analysis

To evaluate valvular heart disease of MRT, the group was divided in patients who received mediastinal RT and in patients who did not. Because of the assumed association between time following irradiation and valvular heart disease, prevalence was also assessed in irradiated patients grouped by number of years between irradiation and cardiac examination (2 to 10 years, 11 to 20 years and >20 years). For analysis of valvular disease patients were categorised into two groups based on severity: none or trace versus more than or equal to mild (≥mild) valvular disease. HLS who underwent valvular replacement were scored according to the degree of severity of valvular disease before surgery. Analysis was performed per patient and for specific types of valvular lesions. Data were expressed as mean/median with standard deviations/range or as percentages. Comparisons of means and medians were performed using the Student's t-test and the Mann-Whitney test respectively, whereas differences in proportions were evaluated by the Chi-Square test.

In the irradiated group, clinical variables possibly associated with valvular heart disease were assessed using regression models. If outcome variables were categorical, logistic regression was performed and results were expressed as odds ratio (OR) and 95%- confidence intervals (CI). If outcome variables were continuous, linear regression models were used and results were expressed as regression coefficients and 95%-CI. For all outcomes, univariate analysis was performed first, after which significant findings were assessed in a multivariate model. Variables used in univariate analysis were current age, sex, BMI, smoking, diabetes, dyslipidemia, hypertension, age at diagnosis, time after treatment, irradiation dose (<40/≥40 Gy), treatment containing chemotherapy and anthracycline containing chemotherapy. In univariate analysis, time after treatment was used as a continuous variable. If this parameter showed a significant univariate association and remained predictive in multivariate analysis, we searched for the optimal cut-off value for this variable.
All analyses were performed using IBM SPSS Statistics version 21. A two-tailed p value < 0.05 was considered statistically significant.

Results

Subjects

Fifty out of 82 HLS were treated with MRT. Patient characteristics and distribution of risk factors for CVD are listed in Table 1. Participants ranged in age from 24 to 79 years and time from MRT varied from 4 to 39 years. Most of irradiated HLS (70%) were treated with a radiation dose of 40 Gy or higher. Between the two groups, no significant differences in mean age and gender distribution were found. However, BMI and number of pack years of smoking were significantly higher in the non-MRT group. Levels of NT pro-BNP were significantly higher in irradiated patients. Also, subjects in the irradiated group were about 9 years younger at diagnosis and received treatment approximately 8 years earlier.

Valvular disease

In the total group of HLS, ≥mild valvular disease was present in 39 of all patients (47.6%) and a total of 65 valves showed abnormalities (24 aortic, 24 mitral, 11 tricuspid, 6 pulmonary). The number of diseased valves exceeds the number of affected patients because more than one valvular lesion occurred in many patients.

Table 1 Patient characteristics. Values are shown as percentages/ mean ± SD (median for pro-BNP and dose of RT)

	MRT (n=50)	No MRT (n=32)	P-value
Current age (yrs)	48 ± 14	48 ± 12	0.870
Male gender (%)	52	59	0.513
BMI (kg/m²)	24.7 ± 4.3	27.7 ± 4.2	0.002
Positive family history of CVD (%)	30	16	0.139
Smoking (pack yrs)	4.6 ± 10.1	11.9 ± 17.7	0.021
Diabetes (%)	4.2	0	0.250
Dyslipidemia (%)	72	72	0.990
NT-proBNP (pg/ml)	155 (27-3633)	45 (9-3270)	0.001
Hypertension (%)	28	28	0.990
Age at diagnosis (yrs)	30 ± 13	39 ± 14	0.003
Time after treatment (yrs)	16.5 ± 8.5	8.1 ± 6.5	0.000
Mediastinal irradiation dose (Gy)	40 (28-44)	-	-
Chemotherapy (%)	70	97	0.003
Anthracycline chemotherapy (%)	52	84	0.192

Valvular disease was more prevalent in irradiated patients (Figure 1). In total, ≥mild valvular disease was present in 61.2% of HLS with MRT (n=30), compared to 31.0% of HLS without MRT (n=9) with an OR 3.51 (95%-CI: 1.32 to 9.30, p=0.01).

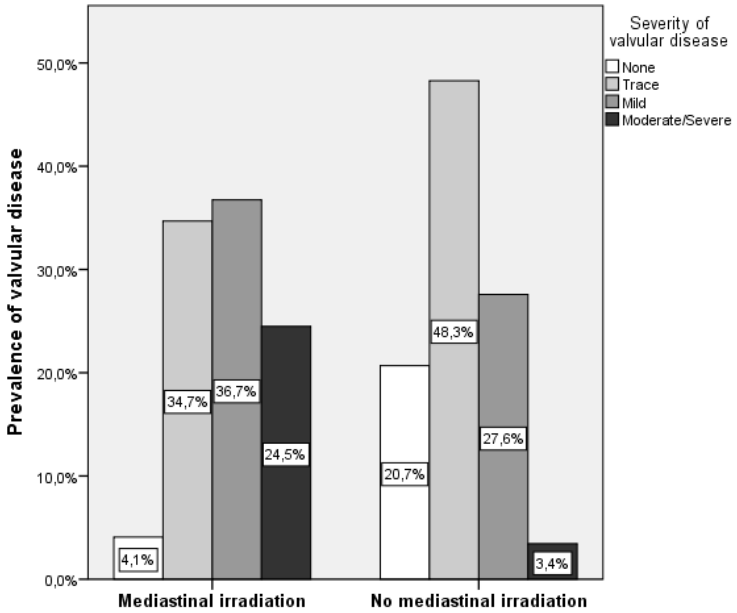

Figure 1 Prevalence of valvular disease graded by severity for subjects in MRT-/non-MRT-group. If multiple valves of one patient were involved, the patient was grouped according to the valve with highest grade of severity.

The degree of severity of valvular dysfunction for separate valves is shown in Table 2.

Table 2 Valvular disease. ***** P-value for differences in ≥ mild valvular disorders between MRT- and non-MRT-group ** Data for tricuspid regurgitation available for 48 subjects in MRT-group (follow-up >20 yrs: 14 subjects) *** Data for pulmonic regurgitation available for 46 subjects in MRT-group (follow-up 2-10 yrs: 11 subjects, >20 yrs: 14 subjects) and 27 subjects in non-MRT-group. Percentages may not add up to 100% due to rounding

Echocardiographic finding	HLS with MRT				HLS with no MRT	p-value*	General population
		Years following irradiation					
	All patients n=49	2-10 yrs n=13	11-20 yrs n=21	>20 yrs n=15	All patients n=29		Prevalence
Aortic regurgitation						0.007	
None (%)	24 (48.0)	10 (76.9)	11 (52.4)	3 (20.0)	26 (89.7)		
Trace (%)	6 (12.2)	1 (7.7)	4 (19.0)	1 (6.7)	1 (3.4)		3.1[11]
Mild (%)	13 (26.0)	2 (15.4)	4 (19.0)	7 (46.7)	1 (3.4)		1.3[11]
Moderate/severe (%)	6 (12.2)	0 (0)	2 (9.5)	4 (26.7)	1 (3.4)		0.15[11]
Mitral regurgitation						0.074	
None (%)	9 (18.4)	3 (23.1)	3 (14.3)	3 (20.0)	12 (41.4)		
Trace (%)	22 (44.9)	5 (38.5)	11 (52.4)	6 (40.0)	12 (41.4)		75[11]
Mild (%)	12 (24.5)	5 (38.5)	6 (28.6)	1 (6.7)	5 (17.2)		13[11]
Moderate/severe (%)	6 (12.2)	0 (0)	1 (4.8)	5 (33.4)	0 (0)		0.54[11]
Tricuspid regurgitation**						0.068	
None (%)	8 (16.0)	5 (38.5)	2 (9.5)	1 (7.1)	13 (44.8)		
Trace (%)	30 (62.5)	8 (61.5)	14 (66.7)	8 (57.1)	15 (51.7)		70[11]
Mild (%)	7 (14.6)	0 (0)	4 (19.0)	3 (21.4)	1 (3.4)		13[11]
Moderate/severe (%)	3 (6.0)	0 (0)	1 (4.8)	2 (14.3)	0 (0)		0.55[11]
Pulmonary regurgitation***						0.847	
None (%)	23 (50.0)	6 (54.5)	8 (38.1)	9 (64.3)	18 (66.7)		
Trace (%)	19 (41.3)	4 (36.4)	12 (57.1)	3 (21.4)	7 (25.9)		17[14]
Mild (%)	4 (8.7)	1 (9.1)	1 (4.8)	2 (14.3)	2 (7.4)		<0.5[14]
Moderate/severe (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		<0.5[14]
Aortic stenosis						0.229	
None (%)	41 (83.7)	12 (92.3)	20 (95.2)	9 (60.0)	27 (93.1)		
Mild (%)	2 (4.1)	0 (0)	1 (4.8)	1 (6.7)	1 (3.4)		<0.5[15]
Moderate/severe (%)	6 (12.3)	1 (7.7)	0 (0)	5 (33.4)	1 (3.4)		<0.5[15]
Mitral stenosis						-	
None (%)	47 (95.9)	13 (100)	21 (100)	13 (86.7)	29 (100)		
Mild (%)	1 (2.0)	0 (0)	0 (0)	1 (7.1)	0 (0)		
Moderate/severe (%)	1 (2.0)	0 (0)	0 (0)	1 (7.1)	0 (0)		

Left-sided valvular regurgitation was most prevalent in HLS with MRT, ≥mild AR in 38.2% versus 6.8% (OR 8.55, 95%-CI: 1.82-40.16, p=0.007) and ≥mild MR in 36.7% versus 17.2% (OR 2.8, 95%-CI: 0.91-8.59, p=0.074), respectively. Mild or greater TR was found in 20.4% (n=10) of HLS treated with MRT, compared to 3.4% (n=1) HLS treated without MRT (OR 7.37, 95%-CI: 0.89-60.95, p=0.064). For MS, a comparison between the two subgroups could not be made since ≥mild MS did not occur in non-irradiated HLS. For all types of valvular disease, prevalence and degree of severity are highest in the group treated more than 20 years before evaluation.

Within the MRT-group, clinical determinants of overall ≥mild valvular disease were current age (OR 1.09 per year, 95%-CI: 1.03-1.17, p=0.004) and time after treatment (OR 1.10 per year, 95%-CI: 1.01-1.21, p=0.026). In multivariate analysis, only current age remained predictive for ≥mild valvular disease (OR 1.08 per year, 95%-CI: 1.01-1.14, p=0.023).

Within the MRT-group, AR could be predicted by current age, hypertension and time after treatment using univariate analysis. In a multivariate model, only time after treatment remained associated with AR (OR 1.13 per year, 95%-CI: 1.01-1.26, p=0.035). A significant cut-off point was found at 15 years after treatment, patients irradiated > 15 years before evaluation shows a 4.70-fold increased odds for AR (95%-CI:1.05-21.03, p=0.043), adjusted for age and hypertension. For TR and AS: hypertension, time after treatment and treatment containing chemotherapy proved to be predictive. Hypertension was also associated with PR. No clinical variables remained associated in multivariate analysis in these valvular lesions. For MR and MS no significant predictors could be identified in univariate analysis in the MRT-group (Table 3).

For the non-MRT group, no significant predictor could be identified for ≥mild valvular disease or other valvular disorders. Time after HL diagnosis was not associated with valvular disorders in this subgroup.

Valvular replacement was performed in 7 (14.0%) of the irradiated patients for a total of 10 valves (Figure 2). Operations performed were 6 aortic valve, 3 mitral valve and 1 tricuspid valve replacements, because of significant aortic stenosis(n=4), aortic regurgitation (AR) (n=2), mitral regurgitation (MR) (n=3) and tricuspid regurgitation (TR) (n=1). No HLS without MRT underwent valvular surgery.

Table 3 Clinical variables associated with valvular disease in univariate analysis in irradiated HLS.

	Univariate analysis		
Parameter	Odds Ratio	95%-CI	p-value
Aortic regurgitation			
Current age (years)	1.09	1.03 to 1.16	0.004
Presence of hypertension	10.00	2.24 to 44.57	0.003
Time after treatment (years)	1.16	1.06 to 1.28	0.002
Tricuspid regurgitation			
Presence of hypertension	6.64	1.47 to 30.00	0.014
Time after treatment (years)	1.11	1.02 to 1.21	0.021
No chemotherapy	10.03	2.13 to 50.26	0.004
Pulmonic regurgitation			
Presence of hypertension	11.00	1.02 to 118.87	0.048
Aortic stenosis			
Presence of hypertension	14.57	2.42 to 87.73	0.003
Time after treatment (years)	1.14	1.03 to 1.26	0.010
No chemotherapy	5.17	1.04 to 25.57	0.044

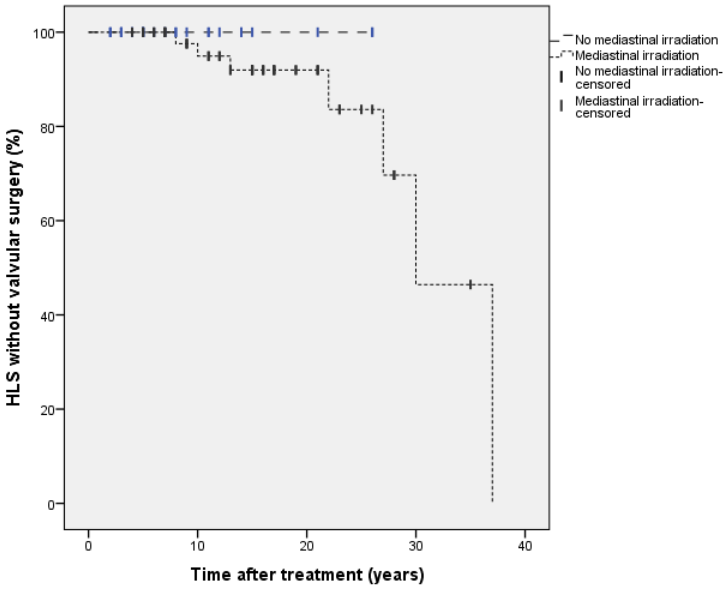

Figure 2 Kaplan-Meier curve showing event -free survival for irradiated and non-irradiated HLS

	0 yrs	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs	30 yrs	35 yrs
Nr. of events	0	0	2	3	3	4	6	6
Nr. of remaining cases (MRT)	50	47	36	23	14	7	2	1
Nr of remaining cases (no MRT)	32	15	9	3	3	2	0	0

The left ventricular- ejection fraction (LV-EF) in HLS with MRT was 55 ± 6.2% compared to 58 ±6.6% in HLS without MRT (mean difference 3.28, 95%-CI: 0.11-6.45, p=0.043) A LVEF of < 50% was present in 15.6% of HLS with MRT (n=7/45) compared to 8% (n=2/25) of HLS without MRT (p=0.37). Diastolic parameters did not differ significantly between HLS treated with and without MRT.

Discussion

This is one of the few studies describing valvular disease in HLS treated with MRT compared to non-irradiated patients. In our cohort of 82 HLS, (asymptomatic) valvular disease was more prevalent in irradiated subjects and increased with time since treatment.

Valvular disease

This study points out that valvular disease is more common in subjects that were treated with MRT, and prevalence increases with follow-up time. This finding was most striking for AR, the most prevalent valvular disorder in our study. More than 20 years after MRT, 75% of patients showed at least a mild severity of AR. Incidence of valvular disease has been reported to increase during the second decade after mediastinal radiotherapy.[5, 8] Heidenreich et al. described almost 300 patients who underwent mediastinal radiotherapy in HLS, and found a clinically important valvular disease in the majority of asymptomatic patients 20 years after irradiation.[6] Furthermore, different rates of AR were found in different studies, depending on the follow-up time of the studies cohort.[5, 14-17]

The second most common valvular disorder encountered was MR. The prevalence of ≥ mild MR was 37% in HLS with MRT, compared to 17% in HLS without MRT. This difference did not reach significancy, however moderate or severe MR was only encountered in HLS treated with MRT (12.2%). Our results are in accordance with studies with comparable follow-up times after MRT.[6, 8, 18]

Increased prevalence of TR has also been reported by Heidenreich[6], at least moderate TR occurred in 4% of irradiated participants compared to 0% for non-irradiated group (p=0.06). The higher prevalence of TR in our irradiated cohort could be due to the fact that we also took a mild degree of regurgitation into account when classifying the presence of TR.

Aortic and mitral stenosis were present in 16.4% and 4% of HLS treated with MRT. The prevalence of these disorders were lower in other studies [6, 8-9, 19], probably due to the fact that we included HLS with previous valvular replacements in this screening study.

Univariate analysis in HLS treated with MRT, showed that hypertension and time after MRT were the most frequent predictors for the different valvular disorders. We could not find an association with other treatment related factors, except for additional chemotherapy which was associated with TR and AS. This 'protective' effect of chemotherapy can be probably explained by the fact that HLS treated with combination of chemotherapy and MRT were treated during more recent years, zo that the effect of chemotherapy is due to the shorter follow-up time in these patients. We also confirm the findings of an earlier study, showing that significant AR did not occur within 10 years after MRT in patients younger than 40 years of age. [6] Furthermore, we also found that a follow up time of at least 15 years after MRT was associated with AR (OR 4.7). These findings underlie the importance of initiating screening programs in HLS in order to identify individuals with severe valvular heart disease.

In valvular disease, the cusp and/or leaflets of valves show fibrotic changes sometimes accompanied by calcification. However, up to now, the pathophysiology of these valvular changes is not very well understood.[20] More common and severe left-sided valvular lesions suggest a possible role of higher pressures of the systemic circulation in pathogenesis of valvular disease.[21] The highest occurrence of aortic valve pathology could be due to the proximity of the aortic valve to the mediastinal RT field.[5] Furthermore, altered arterial elasticity of the aortic root may play a role in AR,[22] since we show that MRT is associated to arterial stiffening.[23]

With regard to systolic function, ejection fraction was slightly lower in irradiated patients. However, the proportion of HLS with an impaired LV-EF of < 50% was not statistically different, suggesting that both MRT and chemotherapy seem to induce some degree of ventricular dysfunction in HLS, as previously described.[24] Time after radiotherapy did not seem to have an influence on the prevalence of impaired LV-EF, concluding that 'old' and modern treatment regimens seem to have the same effect on LV-EF. Furthermore, of 7 HLS treated with MRT with

a LV-EF< 50%, 2 had undergone valvular surgery, and 1 HLS had CAD before this study, so impaired LV-EF could also be a consequence of valvular damage of myocardial infarction. 3/15 (20%) of HLS treated with MRT without valvular surgery in the past who were found to have mild or greater AR, had also an impaired LV-EF <50%. LV systolic function is the most important determinant of postoperative survival in patients with AR, thus HLS with AR and impaired LV-EF should be monitored carefully and surgery should be performed timely.[25]

Screening with echocardiography, a non-invasive and relatively cheap diagnostic procedure, is recommended. The optimal moment to start screening and recommendations for length of screening intervals are difficult to deduct from this small cohort. Our study found significantly higher occurrence of AR 15 years after irradiation. Based on these findings and other studies reviewed before,[26] we would recommend to perform a echocardiogram 10 years after mediastinal RT. Treating physicians should consider cardiac disease at younger ages than in the non-irradiated subjects and patients should be instructed about signs and symptoms of cardiovascular disease. Furthermore, appropriate risk-reducing strategies should be applied; hypertension should be treated, and lifestyle advises should be provided.

Limitations

This study has several limitations. Over the last 40 years, radiation treatment has changed. With techniques like 3-dimensional treatment planning, treatment fields, beam weighting, subcarinal blocks and decreased daily fraction-size, a decrease in cardiac dose-volume irradiation has been achieved.[16] Therefore, our group of irradiated patients with different treatment regimens and time since treatment may not be very well comparable with the effects of current practice. At this moment information on longer periods of follow-up is not yet available for those treated with newer techniques. The benefit of these new methods is unclear.

The cross-sectional nature of this study makes it difficult to assess exact time of origin and time-dependent progression of cardiac disease in the individual patient. Since the reported results are obtained and patients are categorised according to time since irradiation at one point in time, one can only say whether or not (asymptomatic) cardiac abnormalities are present at that point. However, they might have originated several

years before screening, thus actually faster after treatment. Moreover, due to the lack-of follow-up, it remains unclear whether asymptomatic cardiac disease becomes symptomatic over time.
The relative risk of cardiac disease after radiotherapy might have been affected and possibly underestimated by baseline differences between the two groups (the mediastinal RT group was 9 years younger at diagnosis and was followed for 8 more years).
The sample size of this study might have been too small to detect all predictive characteristics of cardiac disease in irradiated subjects.

Conclusion

We found a high prevalence of valvular abnormalities, especially AR, in asymptomatic HLS after mediastinal irradiation. Absence of cardiac disease early after irradiation does not guarantee freedom of cardiac disease later on. Therefore, long time follow up is important. This cardiac follow-up seems even more relevant since the patients at risk are relatively young and have a considerable life expectancy. Screening HLS treated with MRT by echocardiography is recommended starting 10 years after MRT.

References

1. Jemal A, Siegel R, Ward E*, et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71-96.
2. Wethal T, Lund MB, Edvardsen T*, et al.* Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. *Br J Cancer* 2009;101:575-581.
3. Cella L, Liuzzi R, Conson M*, et al.* Dosimetric predictors of asymptomatic heart valvular dysfunction following mediastinal irradiation for Hodgkin's lymphoma. *Radiother Oncol* 2011;101:316-321.
4. Mauch PM, Kalish LA, Marcus KC*, et al.* Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am* 1995;1:33-42.
5. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
6. Heidenreich PA, Hancock SL, Lee BK*, et al.* Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743-749.
7. Kleikamp G, Schnepper U, Korfer R. Coronary artery and aortic valve disease as a long-term sequel of mediastinal and thoracic irradiation. *Thorac Cardiovasc Surg* 1997;45:27-31.
8. 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;22:3139-3148.
9. Greenfield DM, Wright J, Brown JE*, et al.* High incidence of late effects found in Hodgkin's lymphoma survivors, following recall for breast cancer screening. *Br J Cancer* 2006;94:469-472.
10. Perk J, De Backer G, Gohlke H*, et al.* European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012;33:1635-1701.
11. Lancellotti P, Tribouilloy C, Hagendorff A*, et al.* European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:223-244.

12. Lancellotti P, Moura L, Pierard LA*, et al.* European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:307-332.
13. Baumgartner H, Hung J, Bermejo J*, et al.* Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009;10:1-25.
14. Lund MB, Ihlen H, Voss BM*, et al.* Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. *Heart* 1996;75:591-595.
15. Glanzmann C, Kaufmann P, Jenni R*, et al.* Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol* 1998;46:51-62.
16. Kreuser ED, Voller H, Behles C*, et al.* Evaluation of late cardiotoxicity with pulsed Doppler echocardiography in patients treated for Hodgkin's disease. *Br J Haematol* 1993;84:615-622.
17. Gottdiener JS, Katin MJ, Borer JS*, et al.* Late cardiac effects of therapeutic mediastinal irradiation. Assessment by echocardiography and radionuclide angiography. *N Engl J Med* 1983;308:569-572.
18. Gustavsson A, Eskilsson J, Landberg T*, et al.* Late cardiac effects after mantle radiotherapy in patients with Hodgkin's disease. *Ann Oncol* 1990;1:355-363.
19. Glanzmann C, Huguenin P, Lutolf UM*, et al.* Cardiac lesions after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol* 1994;30:43-54.
20. Adams MJ, Hardenbergh PH, Constine LS*, et al.* Radiation-associated cardiovascular disease. *Crit Rev Oncol Hematol* 2003;45:55-75.
21. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum Pathol* 1996;27:766-773.
22. Roberts WC, Ko JM, Moore TR*, et al.* Causes of pure aortic regurgitation in patients having isolated aortic valve replacement at a single US tertiary hospital (1993 to 2005). *Circulation* 2006;114:422-429.
23. van Leeuwen-Segarceanu EM, Dorresteijn LD, Vogels OJ*, et al.* Arterial stiffness is increased in Hodgkin lymphoma survivors treated with radiotherapy. *Leuk Lymphoma* 2012.
24. Lund MB, Kongerud J, Boe J*, et al.* Cardiopulmonary sequelae after treatment for Hodgkin's disease: increased risk in females? *Ann Oncol* 1996;7:257-264.

25. Bonow RO, Carabello BA, Kanu C*, et al.* ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.
26. van Leeuwen-Segarceanu EM, Bos WJ, Dorresteijn LD*, et al.* Screening Hodgkin lymphoma survivors for radiotherapy induced cardiovascular disease. *Cancer Treat Rev* 2011;37:391-403.

8 Progressive muscle atrophy and weakness after treatment by mantle field radiotherapy in Hodgkin lymphoma survivors

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International Journal of Radiology, Oncology, Biology, Physics 2012; 82(2): 612-618

Abstract

Purpose

To describe the damage to the muscles and propose a pathophysiological mechanism for muscle atrophy and weakness after mantle field radiotherapy in Hodgkin Lymphoma (HL) survivors.

Methods and Materials

We examined 12 patients treated by mantle field radiotherapy between 1969 and 1998. Besides evaluation of complaints, the following tests were performed: dynamometry, ultrasound of the sternocleidomastoid, biceps and antebrachial flexor muscles and needle electromyography of neck, deltoid and ultrasonographically affected arm muscles.

Results

Ten patients (83%) suffered from neck complaints, mostly pain and muscle weakness. On clinical examination neck flexors were more often affected than neck extensors. On ultrasound the sternocleidomastoid was severely atrophic in eight patients, but abnormal echo intensity was seen in only three patients. Electromyography of the neck muscles showed mostly myogenic changes, while the deltoid, biceps and antebrachial flexor muscles appeared to have mostly neurogenic damage.

Conclusions

Many patients previously treated by mantle field radiotherapy develop severe atrophy and weakness of the neck muscles. Neck muscles situated within the radiation field show mostly myogenic damage and muscles situated outside the mantle field show mostly neurogenic damage. The discrepancy between echo intensity and atrophy suggests that muscle damage is most likely caused by an extrinsic factor such as progressive microvascular fibrosis. This is also presumed to cause damage to nerves situated within the radiated field resulting in neurogenic damage of the deltoid and arm muscles.

Introduction

The survival of Hodgkin lymphoma (HL) patients has improved significantly during the past decades, with 70-97% of the present cases being cured.[1-3] With longer follow-up, it has become apparent that survivors of HL carry risks for treatment-related side effects that may not manifest until many years later.[4, 5] In patients previously treated by radiotherapy (RT), cardiovascular complications and secondary malignant tumours have the greatest impact on the patients' survival and have been extensively investigated.[6-9]

Less frequently reported late effects are atrophy and weakness of the muscles situated within the radiation fields.[10-14] A considerable number of HL survivors report pain, stiffness or weakness of the muscles; in two reports, 25% and 50% of patients treated by mantle field RT suffer from these problems after a mean of 10 and 19 years of follow-up.[15, 16] Although the mantle field technique has been replaced over the past years by less extensive radiation fields, many patients are still alive who have been treated by this method. As an estimate, 573 HL survivors were treated by RT including the mantle field in the EORTC-GELA H8 Trial from 1993-1999 in 8 European countries.[3] The 10-year overall survival was 92% and 84% for patients with favorable and unfavorable features respectively,[3] leaving about 500 patients still alive who were treated during this period with mantle field RT. Furthermore, in a recent cohort study performed in four centers in the Netherlands, 1415 HL survivors were identified who were treated by mantle field RT between 1965 and 1995.[7]

Muscular complaints of the neck and shoulder areas have long onset latency.[12, 13] Since weakness may be progressive, clinicians dealing with HL survivors will be confronted with these complaints and should have knowledge about the treatment and prognosis of these late effects. The aim of this study is to gain more insight in the pathophysiology and the clinical picture of muscle atrophy in HL survivors treated by the mantle field technique. Furthermore we will give suggestions for the management of these complaints.

Methods and Materials

Patients

Between November 2007 and August 2008, 81 HL survivors were enrolled in a study towards evaluating late sequelae of treatment. Ethical approval has been given by the Institutional Review Board of the St. Antonius hospital, Nieuwegein. All HLS registered at our institution who were free of disease and had a follow-up from diagnosis of HL of more than 2 years were invited to participate (n=113). Nineteen HL survivors were deceased; seven HL survivors did not attend their regular check-ups and could not be traced. Another six HLS declined participation because of old age (n=3), long travelling distance (n=1) or without a specific reason (n=2).

Part of this study is neurological examination including determination of muscle strength. Twenty patients had been irradiated by mantle field radiotherapy (RT) (Table 1). They were all considered candidates for the current study. Three patients were not invited to participate because of recently diagnosed metastatic malignancy (n=2) or end-stage heart failure (n=1). Five of the remaining 17 patients refused participation because of a long travelling distance (n=3), advanced age (n=1) and absence of neck complaints (n=1). Twelve patients (eight women and four men) gave informed consent (Figure 1). The baseline characteristics did not differ from the HL survivors treated by mantle field RT who were not included.

Table 1. Baseline characteristics of the total cohort of 81 HL survivors.

	Hodgkin lymphoma survivors (n=81)		
	Mantle field RT (n=20)	RT on the neck only (n=19)	No RT on the neck (n=43)
Gender, man	10	10	28
Age, years ± SD	53±10	40±11	49±13
RT-dose, Gy ± SD	40±1	36±4	-
Follow-up since diagnosis, years ± SD	23±8	9±5	11±7
Neck muscle weakness, total:	17 (83%)	4 (21%)	4 (9%)
According to FU time from RT:			
- <10 years	-	0/13	
- 10-19 years	6/8	4/6	
- 20-29 years	7/8	-	
- >30 years	4/4	-	

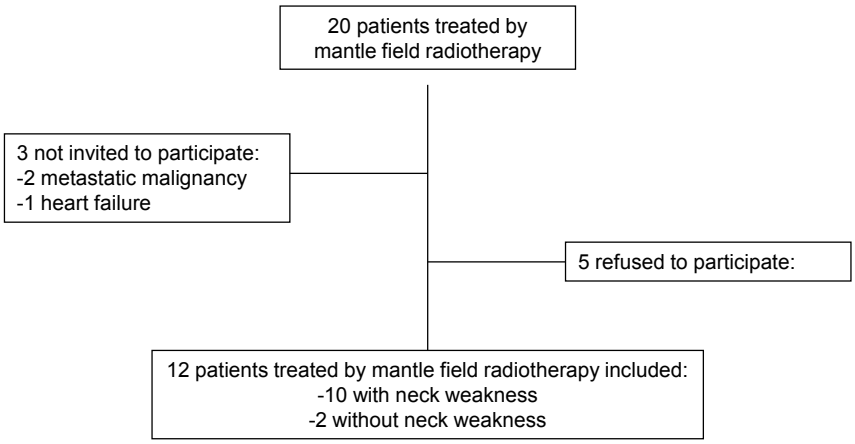


Figure 1. Selection of study population.

Treatment characteristics

The total RT-dose to the mantle field was 40 Gy in 20 fractions of 2 Gy, given in alternating anterior-posterior and posterior-anterior fields. Three patients were also treated with chemotherapy.

Clinical examination

All patients were examined using a standardized protocol. A detailed history was taken about previous neurologic complaints or operations before treatment for HL. Patients were asked to fill in a customized questionnaire including all neurological complaints and functional impairments we had encountered in the whole group. Furthermore, two standardized questionnaires were distributed: the Neck Disability Index (NDI) to enquire about neck complaints[17] and the Checklist Individual Strength-20 (CIS 20) to examine fatigue.[18]

A detailed clinical examination was performed by a senior staff neurologist (OJMV). Strength of the neck flexor muscles was assessed in supine position, the neck extensors in a prone position. Both were graded using the Medical Research Council (MRC) scale.[19]

Muscle strength was also measured with a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, the Netherlands) in five different muscle groups (neck flexors, neck extensors, shoulder abductors, elbow flexors and grip strength). Maximum muscle strength was tested using the 'break' method, in

which the examiner gradually overcomes the muscle strength of the patient and stops at the moment the extremity gives way.[20] Grip strength was measured using the 'make' method. In each patient every muscle group was measured three times and the average score was calculated. Results under p5 of the normal population (for gender) were considered abnormal.[21]

Ancillary investigations

Quantitative muscle ultrasound

Muscle ultrasound examinations were performed of the sterno-cleidomastoid, the biceps and the antebrachial flexor muscles using a standard technique and normal values as described previously.[22, 23] A broadband linear 5-17 MHz transducer (Philips IU22, The Netherlands) was used. All system-setting parameters were kept constant throughout the study (gain 70 dB, compression 55, no adjustments in time gain compensation or focus). For echo-intensities (EI), three consecutive measurements were taken of every muscle and results were averaged. The mean muscle EI was calculated of a region of interest comprising as much muscle tissue without the surrounding fascia using a histogram based grey-scale analysis with 256 grey levels.[23] Muscle thickness was measured with electronic callipers. An increased echo-intensity is indicative of an intrinsic muscle disease.[24]

To compare individual patients and muscles in this study, echo-intensity and muscle thickness were transformed into Z-scores. The Z-score reflects the number of standard deviations a measure deviates from normal, given a certain age and gender. Abnormal EI for individual muscles was defined as a Z-score of more than 2. For muscle atrophy, the same cut-off value was used (Z-score below -2).

Nerve conduction studies and Needle electromyography (EMG)

Electrophysiological examination was performed using standard techniques with a Medelec Synergy EMG system (Viasys, Oxford Medical Instruments, Surrey, United Kingdom). Both nerve conduction studies and needle electromyography were performed according to standardized clinical protocols for the detection of a polyneuropathy and myopathy. Findings were compared to normal values from our centers database. Nerve conduction studies included sensory nerve action potential (SNAP) amplitude and nerve conduction velocity of

both median nerves to the 3rd digit and both superficial radial nerves. Needle EMG of splenius capitis, sternocleidomastoid, and deltoid muscles was performed bilaterally in all patients. Additional needle EMG was performed of the biceps and antebrachial flexor muscles if they showed an abnormal EI on ultrasound.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). One sample t-tests were conducted for comparison between the EI or muscle thickness Z-scores and 0 (the standardized value for certain age and gender).

Results

HL survivors

Baseline characteristics of the HL survivors (n=81) are presented in table 1. Neck muscle weakness revealed by clinical examination had a prevalence of 31%, being highest in the subgroup of patients treated by mantle field RT: 85%. This high percentage was not found in patients treated by RT to the neck only (25%). These patients were treated more recently and with lower RT-dose, reflecting a change of treatment approach in more recent years. The percentage of patients with neck weakness increased form 0% (0/13) in patients irradiated less than 10 years ago to 71% (10/14), 88% (7/8) and 100% (4/4) in patients irradiated between 10-20 years ago, 20-30 years ago and more than 30 years ago, respectively.

Mantle field subgroup

Demographic data of the subgroup of 12 mantle field patients are presented in table 2. Nine patients had other co-morbidities within the radiation field including three women suffering from breast cancer treated by mastectomy.

Neck complaints were present in 10 patients. (Table 3). They reported pain and fatigue in the neck muscles already a few years after RT. Neck complaints were constantly present in two patients and were triggered by activities during which the head had to be held in the same position for more than 30 minutes in eight patients. The patients suffered more frequently of headache than prior to RT; they also experienced pain

Table 2. Demographic characteristics of the 12 HL survivors treated by mantle field RT.
Abbreviations: RT = radiotherapy; MRC = Medical Research Council scale; MOPP = mechlorethamine, vincristine, prednisone, procarbazine; CAD = coronary artery disease; ABV = doxorubicin, bleomycin, vinblastin.

Patient	Age (years)	Sex	Follow-up (years)	Chemotherapy	Co-morbidity	MRC grade neck flexors
1	62	M	36	no	Aorta valve stenosis, RT induced osteoporosis, cervical spine arthrodesis	4
2	58	M	27	no	Aortic valve stenosis, myocardial infarction	3-
3	47	F	27	yes 3x MOPP	Lung fibrosis, thyroid dysfunction	3-
4	60	M	28	No	Atherosclerosis carotid artery, CAD, thyroid dysfunction, osteoporosis, esophageal stricture	2
5	58	F	24	yes 3x MOPP	Breast cancer, thyroid dysfunction, persistent tachycardia	2
6	62	F	16	No	-	3+
7	52	M	40	No	CAD, constrictive pericarditis, thyroid cancer, lung fibrosis	3+
8	47	F	31	No	Breast cancer, thyroid dysfunction, constrictive pericarditis, aortic valve replacement	3+
9	34	F	11	No	Lung fibrosis, thyroid dysfunction	3+
10	50	F	22	No	Breast cancer, CAD, thyroid dysfunction	4-
11	55	M	18	Yes 8x MOPP/ ABV	-	5
12	48	M	24	no	-	5

Table 3. Results of the 12 HL survivors treated by mantle field radiotherapy.
Abbreviations: CIS-20 = Checklist Individual Strength-20; MRC = Medical Research Council scale; EMG = electromyography; SNAP = sensory nerve action potential.

Investigations	Abnormal findings (n)
Questionnaire about neck complaints:	
Neck pain	9 (75%)
Tired feeling in the neck muscles	7 (58%)
Hanging neck	7 (58%)
Thinner neck	9 (75%)
Neck Disability Index	9 (75%)
Severely disabled (score 25-34)	1 (8%)
Moderately disabled (score 15-24)	5 (42%)
Mildly disabled (5-14)	3 (25%)
CIS 20	10 (83%)
Clinical examination (MRC scale)	
Neck flexors	10 (83%)
Neck extensors	6 (50%)
Dynamometry	
Neck flexors	8 (67%)
Neck extensors	4 (33%)
Shoulder abductor	8 (67%)
Elbow flexors	5 (42%)
Antebrachial flexors	2 (17%)
Echointensity	
Sternocleidomastoid muscles	3 (25%)
Biceps muscles	3 (25%)
Antebrachial flexor muscles	3 (25%)
Diameter	
Sternocleidomastoid muscles	8 (67%)
Biceps muscles	1 (8%)
Antebrachial flexor muscles	0
Needle EMG	
Sternocleidomastoid muscles	12 (100%)
Splenius capitis muscles	12 (100%)
Deltoid muscles	10 (83%)
Biceps muscles	2 (17%)
Antebrachial flexors	5 (42%)
Nerve conduction studies	
SNAP amplitude median nerves	1 (8%)
SNAP amplitude radial nerves	5 (42%)
Conduction velocity median nerves	2 (25%)
Conduction velocity radial nerves	1 (8%)

and weakness in the shoulders and arms. Because of these complaints, patients were particularly disabled in the following activities: walking for more than 30 minutes, swimming, lifting the head while in supine position, driving a car, working on the computer, reading and lifting heavy bags. Ten patients were using pain medication for neck pain on a regular basis, or had repeatedly consulted a physiotherapist with satisfactory, but only temporary relief.
On the CIS 20 scale, ten patients had mean scores exceeding 35 points, meeting the criterion for chronic fatigue. On the NDI, the mean and median scores of the total group were 14 and 17 (range, 0-25) (Table 3).

Clinical examination

The ten patients suffering from neck complaints were found to have neck flexor weakness on clinical examination. This was graded 2–4+ on the MRC scale. Neck extension was less often impaired, in six of the twelve patients. In two patients a dropped head syndrome was observed, signifying a grade < 3 paresis on the MRC scale i.e. a disability of the neck extensors to overcome gravity in prone position. On muscle dynamometry muscle weakness in one or more
of the investigated muscles was found in all but four patients (Table 3).

Muscle ultrasound

Muscle ultrasound showed atrophy of the sternocleidomastoid muscles in all but one patient. The mean Z-score of this muscle was -2.27, significantly lower than in the normal population ($p<0.01$). In contrast with the decrease in muscle volume, the EI was rarely above 2 SD in the sternocleidomastoid muscles. Abnormal findings on ultrasound were rare in the muscles located outside the radiation field (Table 3).

Nerve conduction studies

Nerve conduction studies showed abnormalities in 6 patients, of which only one had been treated by chemotherapy (patient nr.11). One patient had low SNAP amplitudes and borderline low conduction velocities of all investigated nerves. Another patient had borderline low amplitude SNAP of the superficial radial nerves on both sides and borderline low nerve conduction velocities of both median nerves. Three patients had low SNAP amplitudes of the superficial radial nerves; in one patient this was present unilaterally. Finally, one patient had isolated low nerve

conduction velocity of the right median nerve at the wrist segment, compatible with a (subclinical) carpal tunnel syndrome unrelated to the radiotherapy.

Needle EMG

Needle EMG showed abnormal findings in the majority of the neck and deltoid muscles. Abnormalities were less prevalent in the biceps and antebrachial flexor muscles (Table 3).

Myogenic changes (small amplitude, short duration motor unit action potentials) were most prevalent in the cervical muscles, occurring in 11 patients (Figure 2). Only one patient showed light neuropathic changes (large amplitude, long duration motor unit action potentials) in the neck muscles. The deltoid muscles showed mostly neuropathic abnormalities (in six patients), while myogenic changes and mixed changes were present in three and one patient respectively. The biceps and antebrachial flexor muscles showed neuropathic damage in all but one patient who were investigated. No spontaneous activity pointing to denervation or myositis was found in any of the patients, but two patients showed myokymia; one in the right deltoid and the other in the right sternocleidomastoid muscle.

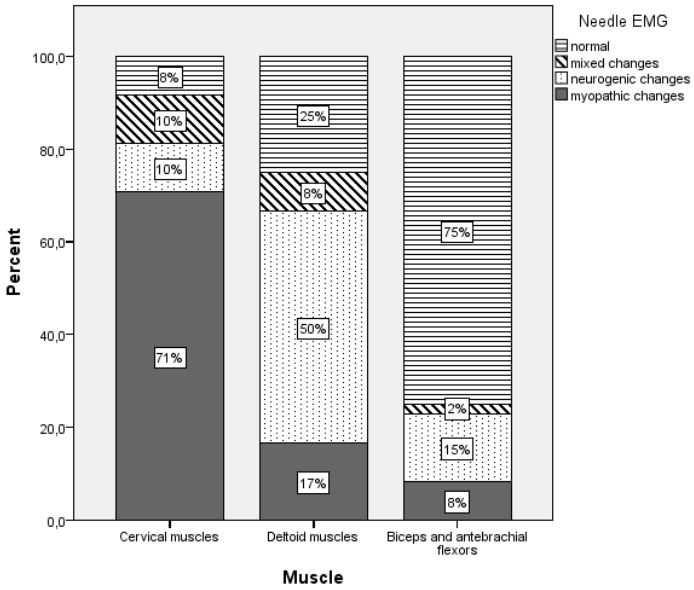


Figure 2. Results of needle EMG.

Discussion

Clinical findings

Neck muscle weakness is a very frequent late complication in HL survivors treated with mantle field RT, occurring in 85% of the patients in our cohort. Patients with impaired neck muscle strength have a large scale of complaints which negatively influence their daily activities and result in increased fatigue scored on the CIS 20 scale. Mantle field RT survivors with preserved neck muscle strength do not experience such severe complaints.

All patients diagnosed with cervical muscle weakness were radiated more than 10 years ago, and most patients (11/12) had an onset latency of more than 15 years. These findings are in line with previous reports describing symptomatic neck muscle weakness mostly occurring more than 10 years after radiotherapy.[13] The progressive character of the muscle damage is shown by the fact that no patients irradiated less than 10 years ago had weakness compared to diminished strength in all survivors treated more than 30 years ago.

Few reports on HL survivors with impaired neck muscle strength describe patients with neck extensor weakness, presenting with a dropped head syndrome.[13, 25] Clinically, we found predominantly neck flexor weakness. When we examined the neck flexors and extensors by needle EMG, all patients showed an equal amount of abnormalities in both muscle groups, suggesting that both the anterior and posterior neck compartments are equally affected by radiotherapy.

Our study is the first one in which systematic testing of all neck muscles has been performed in an unselected group of mantle field treated patients. Typically patients will not consult their physician because of neck flexor weakness as this will manifest in impairment of lifting the head from the pillow or maintaining head position when swimming on the back. These are not very debilitating complaints, in contrast to the dropped head syndrome that occurs when severe damage to the neck extensors develops.[26]

Two mantle-field irradiated HL survivors did not show neck muscle weakness at all. They are both engaged in sport actvities after radiotherapy in which the neck muscles are trained (rowing and water polo). Possibly, muscle strength training may have prevented neck muscle weakness. Interestingly, they showed no late sequelae in other

structures either (cardiac valves, carotid wall, thyroid gland). Apparently, some patients are les vulnerable to radiation induced damage in these tissues, possibly due to genetic differences in radiosensitivity.[27]

Pathophysiology

There is no consensus about the etiology of the muscle atrophy in the few studies performed so far. Several theories have been proposed based on a small number of cases.[10, 11, 13, 28, 29] There have been findings consistent with primary damage to the neurons, the muscles and to extrinsic factors like the vasculature or the connective tissue.

In our study the sternocleidomastoid muscle was severely atrophic in 67% of patients and the group as a whole had a significant lower diameter (and thus volume) of this muscle in comparison to the general population. The discrepancy between this severe atrophy and the mostly normal EI suggests that muscle damage is most likely caused by an extrinsic factor, e.g. the progressive microvascular fibrosis. This has been hypothesized earlier as Fajardo et al showed that capillaries are susceptible to radiation damage.[30]

Needle electromyography of the neck muscles situated in the radiation field showed mostly myogenic changes, with small motor units consistent with the amount of atrophy found. This pattern was also found by others [10, 11, 13] but our study includes the largest number of patients and shows a consistent pattern of myogenic changes in 71% of the muscles entirely situated within the radiation field. Twenty percent of the neck muscles showed neuropathic or mixed changes which can presumably also be explained by vascular injury triggering nerve damage.

The deltoid muscles which are partially situated in the radiation field and the muscles entirely situated outside the radiation field appeared to have mostly neuropathic damage on needle EMG, suggesting primary affection of the nerve roots and brachial plexus which are situated in the radiation field for a long distance. Especially the axillary nerves which innervate the deltoid muscles are prone to injury as they have a smaller diameter and are situated in the axilla which receives a substantial amount of the radiation.[31] Only one of the three patients who were treated by chemotherapy showed neuropathic changes, so this has not substantially contributed to this finding. The myogenic

changes in the deltoid muscles could have been directly caused by radiation to these muscles, as there is some dispersion of radiation as shown in dosimetry studies.[31]

We did not perform muscle biopsy in these patients to confirm our hypothesis. However a myogenic origin of damage in irradiated muscles was shown in four previous reports analyzing muscle biopsies.[10-12] One case report describing the trapezius muscle in a 42 year old HL survivor previously treated by mantel field RT is suggestive of nemaline myopathy[12]. This disorder characterized by muscle atrophy and intracytoplasmatic rod formation in the myofibers, has been observed in a variety of settings (eg. polymyositis, spinal progressive muscle atrophy, acute alcoholic myopathy), when discarding the congenital and familial types which are most frequent. However, it is also a known phenomenon in muscle ageing,[32] possibly suggesting that RT induces accelerated muscle ageing. This disorder was however not described in other HL survivors with muscle weakness. Two other studies performing muscle biopsies in irradiated patients are suggestive of muscular damage.[10, 11] Unfortunately, biopsies were taken from the deltoid muscle, which is not completely situated within the radiation field.[11] Furthermore, Aggarwal et al conclude, after extensive investigations including muscle biopsies, that the etiology of the muscle atrophy is myogenic, but their report had only been presented as an abstract which does not state from which muscles the biopsies were taken.[10] Another case study describes a muscle biopsy from a deltoid muscle in a patient who had been treated by 'whole body RT', a highly uncommon treatment modality for HL. The muscle biopsy revealed chronic neurogenic reinnervation.[13]

Clinical implications

Until now therapy has been focused on supportive care measurements like soft neck collars or surgery (posterior spinal arthrodesis) in more severe cases.[26] Based on our hypothesis that primary vascular injuries may cause myogenic damage in the muscles situated in the radiation field, we recommend training of the affected muscles. This hopefully may promote increased vascularisation of the muscles by forming of collateral vessels, which can contribute to maintaining muscle strength and integrity. Our theory is supported by the fact that the two mantle field irradiated patients without neck weakness perform sports during

which the neck muscles are intensively trained. Moreover, patients visiting a physiotherapist on a regular basis report beneficial results from performing regular training exercises.
Currently, we refer our patients with neck weakness to an academic rehabilitation centre in order to undergo a suited muscle strength training program aiming at reduction of neck complaints and at gain of muscle strength. Further studies are needed in which mantle field irradiated HL survivors are randomized between training on a regular basis versus no training.

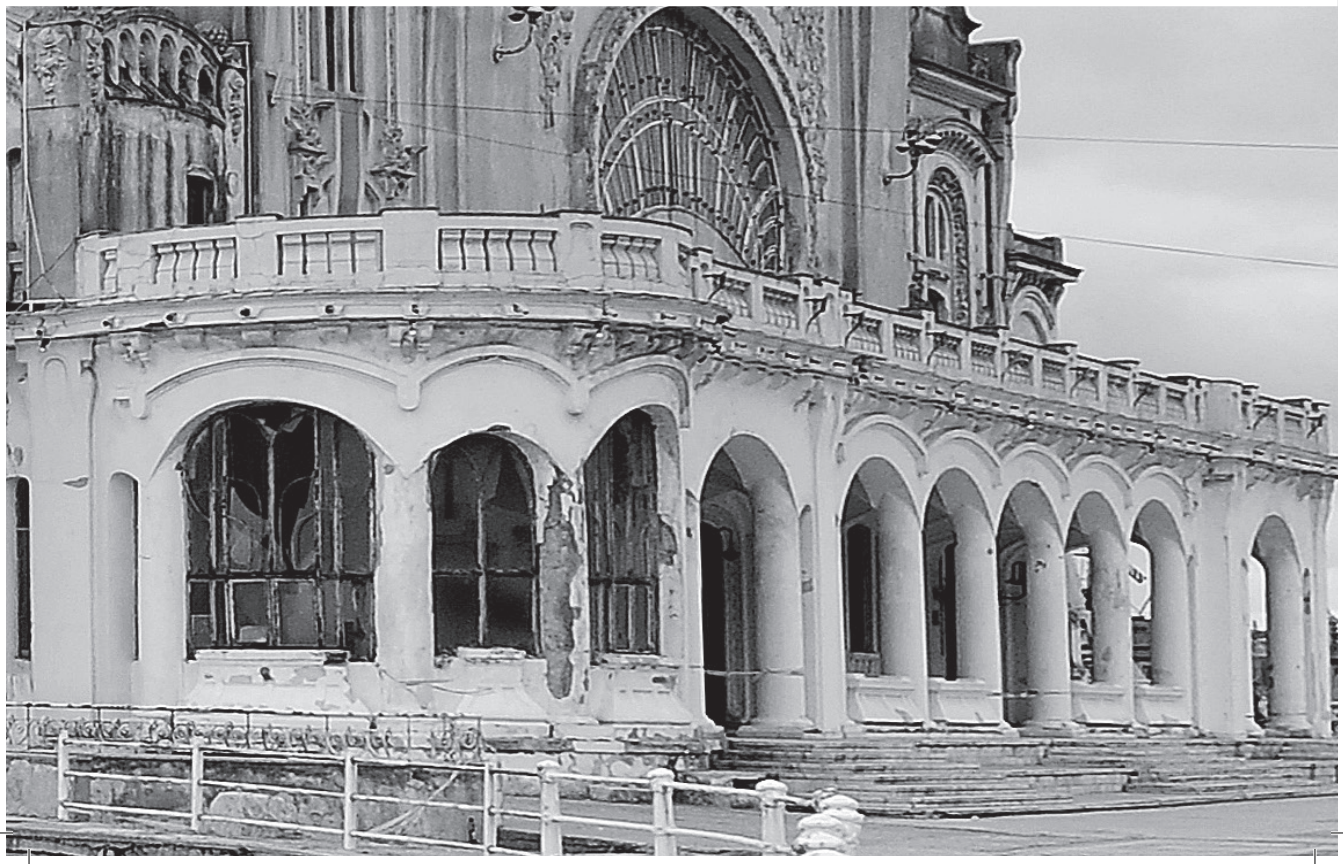
References

1. Klimm B, Eich HT, Haverkamp H*, et al.* Poorer outcome of elderly patients treated with extended-field radiotherapy compared with involved-field radiotherapy after chemotherapy for Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. *Ann Oncol.* Feb 2007;18(2):357-363.
2. Aleman BM, Raemaekers JM, Tomisic R*, et al.* Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* Jan 1 2007;67(1):19-30.
3. Ferme C, Eghbali H, Meerwaldt JH*, et al.* Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med.* Nov 8 2007;357(19):1916-1927.
4. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin Lymphoma treated with radiation therapy. *JAMA.* Dec 3 2003;290(21):2831-2837.
5. Aleman BM, van den Belt-Dusebout AW, Klokman WJ*, et al.* Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol.* Sep 15 2003;21(18):3431-3439.
6. Aleman BM, van den Belt-Dusebout AW, De Bruin ML*, et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood.* Mar 1 2007;109(5):1878-1886.
7. De Bruin ML, Dorresteijn LD, van't Veer MB*, et al.* Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst.* Jul 1 2009;101(13):928-937.
8. Hodgson DC, Gilbert ES, Dores GM*, et al.* Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol.* Apr 20 2007;25(12):1489-1497.
9. Hancock SL, Hoppe RT. Long-Term Complications of Treatment and Causes of Mortality After Hodgkin's Disease. *Semin Radiat Oncol.* Jul 1996;6(3):225-242.
10. Aggarwal S, Amato A. Radiation induced myopathy following mantle field radiation for Hodgkin's disease: a report of 4 cases. *Neurology.* 2007;68(Suppl 1):P05.107 (Abstract).
11. Furby A, Behin A, Lefaucheur JP*, et al.* Late-onset cervicoscapular muscle atrophy and weakness after radiotherapy for Hodgkin disease: a case series. *J Neurol Neurosurg Psychiatry.* Jan 2010;81(1):101-104.
12. Portlock CS, Boland P, Hays AP*, et al.* Nemaline myopathy: a possible late complication of Hodgkin's disease therapy. *Hum Pathol.* Aug 2003;34(8):816-818.
13. Rowin J, Cheng G, Lewis SL*, et al.* Late appearance of dropped head syndrome after radiotherapy for Hodgkin's disease. *Muscle Nerve.* Nov 2006;34(5):666-669.
14. Stone HB, Coleman CN, Anscher MS*, et al.* Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol.* Sep 2003;4(9):529-536.

15. Fossa SD, Holte H, Holmen MM*, et al.* [Long-term effects after mantle field radiotherapy for Hodgkin's lymphoma]. *Tidsskr Nor Laegeforen.* Jan 6 2005;125(1):41-44.
16. Johansson AS, Erlanson M, Lenner P*, et al.* [Late side-effects are common after treatment of Hodgkin's disease. Muscular atrophy following radiotherapy is a neglected risk]. *Lakartidningen.* Jan 7 1998;95(1-2):44-47.
17. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther.* Sep 1991;14(7):409-415.
18. Vercoulen JHMM, Alberts M, Bleijenberg G. [De Checklist Individual Strength]. *Gedrachtstherapie.* 1999;32:131-136.
19. *Medical Research Council. Aids to examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationary Office* 1976.
20. van der Ploeg RJ, Oosterhuis HJ, Reuvekamp J. Measuring muscle strength. *J Neurol.* 1984;231(4):200-203.
21. van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. *J Neurol Neurosurg Psychiatry.* Mar 1991;54(3):244-247.
22. Pillen S, van Dijk JP, Weijers G*, et al.* Quantitative gray-scale analysis in skeletal muscle ultrasound: a comparison study of two ultrasound devices. *Muscle Nerve.* Jun 2009;39(6):781-786.
23. Arts IM, Pillen S, Schelhaas HJ*, et al.* Normal values for quantitative muscle ultrasonography in adults. *Muscle Nerve.* Jan 2010;41(1):32-41.
24. Pillen S, Arts IM, Zwarts MJ. Muscle ultrasound in neuromuscular disorders. *Muscle Nerve.* Jun 2008;37(6):679-693.
25. Bhatia S, Miller R, Lachance D. Neck extensor muscle weakness (Dropped head syndrome) following radiotherapy. *Radiol Oncol.* 2006;40(1):29-33.
26. Gerling MC, Bohlman HH. Dropped head deformity due to cervical myopathy: surgical treatment outcomes and complications spanning twenty years. *Spine (Phila Pa 1976).* Sep 15 2008;33(20):E739-745.
27. Stone HB, McBride WH, Coleman CN. Modifying normal tissue damage postirradiation. Report of a workshop sponsored by the Radiation Research Program, National Cancer Institute, Bethesda, Maryland, September 6-8, 2000. *Radiat Res.* Feb 2002;157(2):204-223.
28. McFarlane VJ, Clein GP, Cole J*, et al.* Cervical neuropathy following mantle radiotherapy. *Clin Oncol (R Coll Radiol).* Dec 2002;14(6):468-471.
29. Gillette EL, Mahler PA, Powers BE*, et al.* Late radiation injury to muscle and peripheral nerves. *Int J Radiat Oncol Biol Phys.* Mar 30 1995;31(5):1309-1318.
30. Fajardo LF, Berthrong M. Vascular lesions following radiation. *Pathol Annu.* 1988;23 Pt 1:297-330.

31. Amies C, Rose A, Metcalfe P, *et al.* Multicentre dosimetry study of mantle treatment in Australia and New Zealand. *Radiother Oncol.* Aug 1996;40(2):171-180.
32. Tomonaga M. Histochemical and ultrastructural changes in senile human skeletal muscle. *J Am Geriatr Soc.* Mar 1977;25(3):125-131.

9 | Summary



Cure can be achieved with current treatment modalities in most patients with Hodgkin Lymphoma (HL). For many years, focus of initial therapy is reduction of long-term complications, mainly secondary malignancies and cardiovascular diseases. This thesis focuses on cardiovascular complications in Hodgkin Lymphoma survivors (HLS). The development of cardiovascular complications is mostly related to mediastinal radiotherapy. Although numerous studies describe cardiovascular complications after radiotherapy, guidelines for comprehensive cardiovascular screening and treatment of risk factors in HLS are still lacking.

In **chapter 2,** the available data on different screening modalities for cardiovascular disease are summarized and a proposal for a cardiovascular screening program in HLS treated with radiotherapy is given. Part of this proposal is screening for coronary artery disease (CAD) starting five years after radiotherapy in HLS 45 years or older and in younger HLS with two or more traditional cardiovascular risk factors. Screening for CAD can be delayed till 10 years after radiotherapy in younger patients with one or less traditional risk factors. Modern imaging techniques like coronary artery (CAC) score or CT-angiography may be the preferable methods for screening. HLS with CAD can remain asymptomatic for a long time due to nerve damage caused by radiotherapy. Therefore, in HLS with CAD on modern imaging techniques, additional testing for the detection of the severity of CAD should be performed, even in the absence of complaints. Valvular disorders can be most properly evaluated by echocardiography starting 10 years after radiotherapy in all HLS. Arrhythmias or conduction abnormalities can be detected by electrocardiography, which should be performed at each cardiovascular screening moment. Repeating these screening tests every five years is advised. Furthermore, HLS should be repeatedly instructed about signs and symptoms of cardiovascular disease and should contact their treating physician in case of complaints. Furthermore treating physicians should be aware of the risks of cardiovascular disease in HLS. Traditional cardiovascular risk factors should be carefully monitored and treated, considering patients treated with RT as high risk patients for cardiovascular disease, who should be treated according to guidelines for secondary prevention.

Arterial stiffness has been shown to be an early marker of cardiovascular disease and a surrogate marker for cardiovascular mortality in several high risk populations like patients with diabetes and chronic kidney disease. In **chapter 3,** arterial stiffness is described for the first time in patients treated with radiotherapy. Two different parameters of arterial stiffness are measured: the carotid-femoral pulse wave velocity (PWVcf) and the common carotid artery (CCA) distensibility coefficient (DC). A high PWVcf and a low DC are indicative of stiffer arteries. Overall, PWVcf was not significantly higher in HLS with radiotherapy to the aorta, compared to HLS without radiotherapy to the aorta or to controls. Age at radiotherapy proved to be a significant predictor of PWVcf. PWV was significantly higher in patients treated with radiotherapy at age > 40 years (8.54 m/s) than in patients irradiated at younger age (7.14 m/s) and controls (6.91 m/s), even after adjusting for traditional risk factors. Similar results were found in HLS irradiated on the CCA. The lowest CCA-DC was found in HLS treated with radiotherapy at an age of > 35 years. In general, radiotherapy is associated with increased arterial stiffness. The effect of radiotherapy seems most prominent when RT is administered at older age (above 35-40 years).

PWVcf had not been measured previously in patients treated with radiotherapy. The optimal technique for measuring PWVcf has still to be determined. Therefore, two devices (SphygmoCor and Vicorder) for measuring PWVcf were compared in **chapter 4** in a group of 38 healthy individuals. The SphygmoCor is based on applanation tonometry and the Vicorder uses an oscillometric technique to measure the PWV over the carotid-femoral trajectory. The Vicorder is a new device, designed to be easy in daily use and less operator-dependent. The Vicorder was compared to the widely used SphygmoCor. Intra-operator reproducibility of each instrument and comparison between the two devices, assessed by the Bland-Altman method, showed better properties for the SphygmoCor device. This device has subsequently been used to measure PWV in HLS (chapter 3).

Intima media thickness (IMT) of the carotid artery is a strong predictor of stroke in high risk populations. Together with the presence of plaque and other traditional cardiovascular risk factors, IMT can be used to

stratify patients in high/low risk categories for the development of cardiovascular disease. The results of IMT and plaque in 82 HLS and 40 control subjects are described in **chapter 5.** HLS treated with radiotherapy on the CCA had higher unadjusted IMT (0.582 mm) than HLS treated without radiotherapy (0.538 mm) and controls (0.530 mm). After fitting a multiple mixed model, IMT was highest (0.631 mm) in the HLS treated with RT more than 15 years before screening. In multivariable analysis the following predictors of IMT were identified: follow-up time from radiotherapy, current age, abdominal circumference and pack years of smoking. The occurrence of plaque was also most prevalent (12/20 patients) in the HLS treated with radiotherapy on the CCA more than 15 years before. In multivariable logistic regression analysis, age and female gender proved to be significant factors too. In conclusion, HLS treated with radiotherapy to the neck are at increased risk of developing subclinical atherosclerosis of the CCA, the risk increasing with increasing follow-up time from radiotherapy. Due to the small differences in radiotherapy dose used in this group of HLS, we could not demonstrate an effect of radiotherapy dose on IMT or plaque.

CAC-score measurements have been performed in 75 HLS, of which 46 patients had been treated with mediastinal radiotherapy (MRT). The results of the CAC-score measurements and clinical characteristics of these patients are described in **chapter 6.** Significantly increased CAC-scores (i.e. CAC-scores >75th percentile for age and gender of the normal population) were found in 41.3% of HLS treated with MRT, compared to 10.3% in non-irradiated HLS. Most significantly increased CAC-scores were observed in the 35 HLS treated with MRT more than 10 years before screening (51.4%). The percentage HLS with a CAC-score > 75th percentile was 9.1% in the HLS treated with MRT less than 10 years ago, comparable to 10.3% in the non-MRT group. HLS treated with MRT and CAC-score > 75th percentile had more traditional cardiovascular risk factors (median 3) than HLS treated with MRT with a CAC-score < 75th percentile (median 2).

Chapter 7 describes the findings from echocardiography in 82 HLS, of which 50 were treated with MRT. Overall, during a median follow up of 13.4 years, severe valvular heart disease occurred in 24.5% of

the irradiated HLS patients compared to 3.4% of non-irradiated HLS (p=0.016). Aortic and mitral insufficiencies were most frequently observed. Follow-up time after MRT and hypertension seem to be associated with an increased risk of valvular disorders, especially aortic regurgitation. HLS treated with MRT more than 15 years ago, have a significant 4.70-fold (95%-CI: 1.05-21.03, p=0.043) increased odds for AR than HLS treated with MRT shorter than 15 years ago, after adjusting for age and hypertension. Valvular replacement was performed in 14.0% of the irradiated patients for a total of 10 valves, comparing to 0 non-irradiated HLS.

During the extensive cardiovascular work-up, a remarkable phenomenon was reported by HLS. They had various complaints of their neck muscles, varying from pain to weakness. In order to reveal the pathogenesis of these neck muscle complaints in HLS, 12 HLS treated with mantle field radiotherapy underwent a thorough investigation, described in **chapter 8.** Besides a precise description of their complaints, additional tests were performed, such as dynamometry, ultrasound of the sternocleidomastoid, biceps and antebrachial flexor muscles and needle electromyography of neck, deltoid and ultrasonographically affected arm muscles. Ten HLS reported neck complaints, most had neck pain and muscle weakness which sometimes were very invalidating. On clinical examination neck flexors were more frequently affected than neck extensors. Patients suffering from neck extensor weakness were most invalidated due to pain. One patient even had a dropped head syndrome. Additional investigations showed that muscles situated within the mantle radiation field mostly showed myogenic damage; muscles situated outside this field showed mostly neurogenic damage. A discrepancy was found between echo-intensity and muscle atrophy, suggesting that muscle damage is most likely caused by an extrinsic factor such as progressive microvascular fibrosis, which can also cause damage to nerves situated within the mantle field.

10 Discussion

This thesis focuses on the early detection of cardiovascular and neurological abnormalities in Hodgkin Lymphoma Survivors (HLS) in a relatively small population of 82 patients and 40 controls and in a cross-sectional setting. So far, most studies have described symptomatic cardiovascular diseases in terms of clearly defined end points. Contrary to the guidelines with regard to screening for secondary malignancies and hypothyroidism which have been implemented widely, no well designed screening programs for cardiovascular disease have been designed in HLS. Radiotherapy regimens for Hodgkin Lymphoma (HL) have changed substantially during the last decades, less intensive treatment modalities being introduced. From the studies presented in this thesis, one may conclude that especially patients who received radiotherapy before 1995-2000 (more than 10-15 years ago) are prone to cardiovascular events. For these patients, a screening program is urgently needed. First, we discuss the changes in the treatment modalities for HL and the limitations of our study sample with regard to the recommendations for screening. Then, we discuss the results of the different cardiovascular screening modalities performed in this group of HLS. Based on these findings we suggest a cardiovascular screening program for HLS.

Changing treatment modalities in HL patients

In our study, HLS survivors were treated between 1969 and 2005 with different first line regimens. The findings from the studies presented in this thesis should be judged in light of the treatment modalities and their changes over the past decades. Especially radiotherapy has been adapted to less extensive fields and to lower dose. However, there were no uniform treatment strategies for certain periods of time. As of the early 1990's, most of the patients described in our study were treated within randomized controlled trials designed by the European Organisation for Research and Treatment of Cancer (EORTC). These studies, aiming at the optimal treatment for HL patients, compared old with new treatment strategies and have been described in detail elsewhere.[1] As a consequence of participation in these trials, some HL patients were treated with extensive field radiotherapy until the late 1990's.[2] Furthermore, the highest radiotherapy dose of 40 Gy was still used in 3 of 13 patients treated with radiotherapy from 2000 until 2005. Before the early 1990's, HL patients were mostly treated with extensive

field radiotherapy. However in our study, of the 28 patients treated with radiotherapy before 1993, 11 received involved field radiotherapy (mostly radiotherapy to the mediastinum only, n=9 patients). Also chemotherapy regimens were modernised, most HL patients treated during recent years receiving ABVD treatment. However, older schemes like EBVP were also part of EORTC trials until early 2000 (see abbreviation list for explanation of chemotherapy regimens). MOPP containing chemotherapy was abandoned in our study population in 1997. Because of this variation in treatment modalities over the years, it is difficult to differentiate whether certain types of treatment or follow-up time from treatment determine the long-term outcomes of HLS in our studies.

In order to better illustrate the characteristics of the different treatment regimens in our HLS, we will describe in more detail the different treatment modalities (Table). Extensive radiotherapy fields (currently abandoned) were used in 20 HLS described in this thesis: mantle field radiotherapy (n=18) and subtotal nodal irradiation (n=2). Involved field radiotherapy was given in 35 HLS: radiotherapy to the mediastinal and

Table. Patients and treatment characteristics in all 82 HLS described in this thesis.

Treatment regimens in HL survivors n=82	Patient characteristics in HL survivors n=82	
	Age at HL diagnosis years (range)	Follow-up from HL diagnosis years (range)
All HLS (n=82)	33.4 (12-69)	13.4 (2-39)
Chemotherapy only (n=27)	39.1 (18-69)	8.4 (2-26)
Chemotherapy and radiotherapy (n=39)	30.6 (16-61)	14.1 (2-37)
Radiotherapy only (n=16)	29.5 (12-65)	20.2 (11-39)
Extensive field radiotherapy (n=20)	28.9 (12-65)	22.7 (11-39)
Involved field radiotherapy (n=35)	31.1 (16-61)	11.9 (2-28)
Radiotherapy dose ≥ 40 Gy (n=37)	28.2 (12-65)	19.4 (5-39)
Radiotherapy dose < 40 Gy (n=18)	34.6 (16-61)	8.6 (2-19)
Anthracyclin containing chemotherapy (n=54)	34.6 (16-69)	9.0 (2-28)
Chemotherapy without anthracyclin (n=12)	30.9 (21-51)	21.8 (11-39)
ABVD (n=26)	38.3 (18-61)	5.5 (2-10)
MOPP/ABV (n=16)	32.6 (18-69)	13.5 (10-19)
BCVPP (n=8)	32 (21-49)	19 (16-21)
MOPP (n=7)	27.1 (17-51)	27.6 (23-37)
EBVP (n=5)	27.2 (24-32)	6 (5-8)
BEACOPP (n=2)	34.5 (24-45)	11 (7-15)
OPPA (n=2)	17 (15-17)	15 (14-16)

cervical lymph regions (n=15), mediastinal region only (n=14), cervical region only (n=4), inverted Y technique (para-aortic and inguinal regions) and axillary region only (n=1 for each). Two-thirds of patients treated with radiotherapy received 40 Gy (n=35) or more (n=2; 42 Gy and 44 Gy respectively) and only one third was treated with 36 Gy (15 patients, one with 37 Gy) or less (n=2; 20 Gy and 28 Gy respectively).
Currently, ABVD is the first-line chemotherapy regimen of choice in HL patients. In our cohort 26 patients were treated with this regimen, the other chemotherapy regimens are described in the Table. 54 HLS have been treated with anthracycline containing chemotherapy: 47 as first line treatment for HL, 4 as treatment of HL relapse and 1 patient because of secondary breast cancer. The mean cumulative anthracycline dose was 304 mg/m^2 (range 100-660 mg/m^2). This dose was calculated taking into account all anthracycline containing treatments (relapse and treatment for secondary malignancy).
Of the 82 included HLS, 12 patients were treated for a relapse of HL. During recent years (mean follow-up from relapse until current study: 5 years), relapses were treated with DHAP-VIM-DHAP chemotherapy followed by BEAM and autologous stem cell transplantation in 7 HL patients (4 were previously treated with ABVD chemotherapy only, two with ABVD and involved field radiotherapy and one with EBVP chemotherapy only). A relapse after initial treatment with radiotherapy only occurred in 3 HL patients. All were treated with ABVD or MOPP/ABV for their relapse. One patient previously treated with MOPP and involved field radiotherapy was treated with 6 cycles of ABVD for the HL relapse in 1984. One patient previously treated with EBVP and involved field radiotherapy was treated with 6 cycles of MOPP/ABV for the HL relapse.
Eight patients were diagnosed with a secondary malignancy, six before and two during the course of this screening study. Four women suffered from breast cancer, three being previously treated with mantle field radiotherapy and one patient with radiotherapy on the mediastinum. Two other patients were diagnosed with a lung carcinoma and two with a thyroid carcinoma, all being treated with radiotherapy to the mantle field or mediastinum. The median interval between radiotherapy and the diagnosis of secondary malignancy was 17 years.
Because of the different treatment regimens over the years, these patients form a heterogeneous group, but are a typical HLS population

that most haematologists encounter in their practice. Patients treated longer ago not only have a longer follow-up time but were also treated differently (with radiotherapy only, more extensive radiotherapy fields, higher radiation dose and older chemotherapy regimens), see Table. Due to the well-known late effects of treatment, haematologists keep following these patients on the outpatient clinic, without exactly knowing what they should be looking for in the individual patient. Screening guidelines for secondary cancers and hypothyroidism have been implemented, but there are no evidence based recommendations on how to monitor HLS for other late cardiovascular disorders and neurological diseases. There are especially no patient tailored guidelines on what investigations are to be performed in the different groups of HLS based on the treatment modalities they were exposed to. There is no data on which factors should be taken into account when deciding how to screen HLS, like gender, cardiovascular risk factors, the occurrence of other late complications of treatment (like hypothyroidism), age at treatment, etc.

We hope that the data from this cohort HLS will contribute to a better understanding of the prevalence of sub-clinical cardiovascular and neurological damage in HLS, despite treatment with various radiotherapy and chemotherapy regimens. Furthermore, risk factors for these late effects are studied; their identification will hopefully facilitate the recognition, closer monitoring or, if necessary, treatment of individuals at high risk of developing symptomatic disease. The final aim is to improve the long term quality of life and survival of HL patients.

Vascular disease

Arterial stiffness

We show for the first time that arterial stiffness is associated with radiotherapy. Based on animal studies and human histological research we hypothesise that the pathophysiology of arterial stiffening after radiotherapy is multifactorial. First, arterial stiffening can be a consequence of nitric oxide (NO)- and prostacyclin-mediated endothelial dysfunction which was shown to occur early [3-4] and probably still is present years after radiotherapy.[5] Furthermore, atherosclerotic lesions of the arterial wall can contribute to the stiffening of arteries, since fibrous tissue deposition, disruption of the internal elastic membrane

and increased proteoglycan content were found in irradiated vessels.[6-8] We found that arterial stiffness was most increased in HLS irradiated treated at older age. This can be explained by the further decrease in NO levels by radiotherapy [4] in older subjects who already have lower levels of NO than younger healthy subjects.[9] Furthermore, RT can accelerate atherosclerosis which is more often present in older subjects.[10]

Based on these findings and on the fact that follow-up time from radiotherapy was not associated with arterial stiffness, we hypothesise that arterial stiffening probably occurs early after radiotherapy. This hypothesis could have two implications:

First, HL patients aged 35-40 or older at diagnosis (half of HL patients, since median age at diagnosis is 38 years) should be treated with a patient-tailored approach. Patients with high cardiovascular risk based on traditional cardiovascular risk factors, arterial stiffness parameters might best be treated with chemotherapy only. For example, a 45 years old HL patient with 2 cardiovascular risk factors (for example smoker and diagnosed with untreated hypercholesterolemia) and a PWV above the reference value for age and gender should be treated with an intensive chemotherapy regimen only ($BEACOPP_{escalated}$ for example). In contrast, another HL patient of 45 years old with the same HL risk-factors, but without cardiovascular risk factors and a normal PWV, might best be treated with chemotherapy (for example ABVD) and involved field radiotherapy.

Second, arterial stiffness measurements can be a potential screening method after radiotherapy to detect which HLS are at increased risk of developing cardiovascular disease. However, we do not recommend screening irradiated HLS with arterial stiffness parameters, since no therapeutic intervention can be initiated that improves the arterial stiffness. Hypertension and other risk factors for cardiovascular disorders should be treated in irradiated HLS, independently of the outcome of arterial stiffness measurements.

Our findings need to be confirmed in HLS treated with modern regimens. However, since follow-up time from radiotherapy and radiotherapy dose were not associated with PWV or DC, these findings are expected to be comparable in HLS treated with modern techniques only. Of course, prospective trials are needed to assess the predictive value of arterial stiffness in the occurrence of cardiovascular events

in HLS. Randomized controlled trials are needed to assess the best cardiovascular- and HL-risk factor- based treatment strategy of HL. Current HL treatment strategies based on HL prognostic factors and PET guided decision making should be compared to a strategy in which cardiovascular profile is also taken into account. At diagnosis of HL, a randomisation should take place for standard HL treatment without considering the cardiovascular risk profile, compared to a cardiovascular-tailored approach as suggested in the example above.
Furthermore, individual results of single PWV measurements should be interpreted with care; since it was shown in reproducibility studies that differences in PWV in the same subject can vary up to 1.5 m/s.[11-13] In order to improve accuracy of the obtained PWV value which would classify HLS in the low/high risk group for CVD, the mean of three PWV measurements should be taken into consideration.

Atherosclerotic disease
The two studies evaluating atherosclerotic disease (carotid and coronary artery disease) show similar findings. Both demonstrate an association between radiotherapy and atherosclerotic disease. Atherosclerosis was most prevalent when HLS were followed for 10-15 years or more form radiotherapy. This is consistent with findings from studies describing symptomatic cardiovascular disease,[14-16] suggesting that radiotherapy has a prolonged effect on atherosclerosis. As discussed above, it is difficult to differentiate between the effects of follow-up time from radiotherapy and the older radiotherapy techniques as the true risk factors for atherosclerosis. Further follow-up of this cohort and other studies in a larger number of recently treated HLS are needed to clarify this issue. Another consistent finding in these two studies is that traditional risk factors for cardiovascular disease are predictors of IMT, plaque and CAC-scores. This in concordance with other studies [17-18] and underlines once more the importance of treating hypertension, hypercholesterolemia and encouraging smoking cessation and losing weight in HLS.
Based on our results, screening HLS for sub-clinical atherosclerotic disease (intima media thickening of the common carotid artery, plaques of the neck arteries or coronary artery calcium) seems reasonable starting 10 years after radiotherapy. This cross-sectional study is not designed to identify the best screening method for the

prediction of cardiovascular disease. Of course, in patients treated with radiotherapy to the neck only IMT/plaque should be monitored. In HLS with radiotherapy to the mediastinum only, screening by imaging of the coronary arteries should be performed. In HLS treated with radiotherapy to both cervical lymph nodes and mediastinum, further follow-up of this cohort of HLS is needed in order to identify the best parameter to be monitored.

From the studies presented in **chapters 4 and 5** we cannot distillate the clinical consequences of the detection of sub-clinical atherosclerotic disease. With regard to asymptomatic carotid artery stenosis, the treatment of choice is still a matter of debate. [19-20] In the guidelines of the American Heart Association/American Stroke Association the advantages of current medical therapy are underlined in contrast to the small absolute risk reduction of stroke in patients treated by revascularisation techniques.[19] Therefore, a careful selection of asymptomatic patients who should be treated with carotid revascularisation is advocated. [19] In contrast, guidelines from the Society for Vascular surgery recommend carotid endarterectomy (CEA) as first-line treatment for most patients with asymptomatic carotid stenosis of 60 to 99 percent.[20] In the current guidelines, there are no recommendations for the management of asymptomatic carotid artery stenosis in patients treated with radiotherapy to the neck.[19] A recent meta-analysis in irradiated patients showed that stenting and CEA are feasible revascularization techniques with low risk for any cerebrovascular adverse effects.[21] Although patients undergoing CEA had more temporary cranial nerve injury, higher rates of late cerebrovascular adverse effects and restenosis were identified after carotid stenting.[21] HLS treated with radiotherapy to the neck who are found to have asymptomatic carotid artery disease have other characteristics than the patients on which the guidelines are based on.[22] They are younger at diagnosis of atherosclerosis and therefore can benefit longer from the effects of revascularisation strategies. Furthermore, atherosclerosis is thought to be accelerated by radiotherapy, therefore HLS may already benefit from aggressive (medical) therapy at diagnosis of atherosclerosis, even before a significant stenosis has occurred.

The clinical consequence of significantly increased CAC-scores is even more unclear. Until now it has not been proven that initiating

pharmacologic therapy in asymptomatic patients with CAC improves outcomes. However the studies performed on this subject did not include irradiated patients and mostly had a short follow-up.[23-25] CAC was shown to be highly sensitive and moderately specific for the presence of ≥50 percent angiographic coronary stenosis.[26] Therefore additional diagnostic studies are probably warranted in order to detect the degree and significance of coronary artery stenosis. This is particularly important since HLS with significant CAD can remain asymptomatic for a long time.[27] Subsequently, the best treatment strategy can be instituted.

This thesis thus raises several questions which can only be answered by prospective studies:

- Should HLS in which plaque or a high IMT was detected in the neck arteries be followed with ultrasound for the timely detection of significant carotid artery stenoses?
- How often should follow-up studies be performed?
- Should HLS with sub-clinical carotid atherosclerosis and no significant stenosis receive aggressive medical treatment with platelet aggregation inhibitors, statins and antihypertensive agents even in the absence of hypercholesterolemia/hypertension?
- What should be done if asymptomatic carotid artery stenosis has occurred (aggressive medical therapy, percutaneous stenting or surgical intervention)?
- What are the consequences of the detection of a significantly increased CAC-score during follow-up?
- Should HLS in which a significantly increased CAC-score was found be tested with additional tests (stress-tests/coronary angiogram) in order to detect clinically relevant CAD?
- How often should HLS be screened for sub-clinical CAD? Should HLS with a significantly increased CAC-score (without proven significant CAD) be screened more often than HLS with a not-significantly increased CAC score? Can HLS with a CAC score of 0 be screened less frequently?
- What is the optimal screening method?
- Should HLS with sub-clinical coronary atherosclerosis receive prophylaxis with platelet aggregation inhibitors or lipid lowering drugs even in the absence of hypercholesterolemia?

Furthermore, research should be initiated on the role of atherosclerosis-screening in HL patients at diagnosis of HL. As has been shown by others[18], HLS seem to develop cardiovascular disease at an earlier stage after radiotherapy if they are older at radiotherapy. This is possibly caused by accelerated vascular disease by radiotherapy.[10, 18] We were not able to confirm these findings in our study, since older age at radiotherapy was not associated with IMT, plaque or CAC-score. However, since arterial stiffness was associated with age at radiotherapy and taking into consideration the data from the literature, it seems reasonable to us that a detailed cardiovascular risk profile should be determined at diagnosis of HL. This cardiovascular profile can be based on traditional cardiovascular risk factors, arterial stiffness and/or atherosclerotic parameters. The best combination of tests should be determined by further research in HLS, as is currently being investigated in other high-risk populations like the SMART-study cohort.[28-29] In HL patients with a high-risk profile on cardiovascular screening, treating haematologists can consider initiating HL treatment without radiotherapy, as patient-tailored HL treatment has been frequently advocated by experts in this field.[30]

Cardiac disease

In addition to coronary artery disease we looked into other cardiac abnormalities in HLS. When screening for valvular disease, we found that nearly half (47.6%) of all patients had mild, moderate or severe valve abnormalities. Valvular disease was more prevalent in HLS treated with mediastinal radiotherapy (61.2 %) when compared to HLS treated without mediastinal radiotherapy (31%). Left-sided valvular regurgitations, together with tricuspid valve regurgitation were the most common valvular disorders. These results are similar to recent studies in larger groups of HLS.[31-32] Furthermore, the prevalence of valvular disease increased with time after radiotherapy, as also described by others.[32-33]

Based on these findings and on the available literature summarised in **chapter 2** we suggest performing a first screening echocardiography 10 years after mediastinal radiotherapy. Identifying even mild valvular disorders or functional cardiac abnormalities should prompt closer follow-up by cardiologists and treatment of associated risk factors and symptoms at an early stage.

We did not find any relevant abnormalities by screening electrocardiography (ECG), so the importance of this screening modality remains unknown (data not shown). Older studies show a high rate of abnormalities on ECG [34-35], while a new study also showed mostly normal ECG's in HLS [32], suggesting that more recently treated HLS are not as much as risk of developing arrhythmias or conduction system abnormalities.

Neurological disease

This is the first study that systematically investigates the burden and pathophysiological mechanism of radiation-induced muscular damage. Based on clinical findings, results of muscle ultrasound and needle electromyography of muscles situated within and outside the radiation field, we conclude that damage is most likely caused by an extrinsic factor such as progressive microvascular fibrosis. When considering a vascular injury as the primary cause of myogenic damage, we suggest training of the affected muscles, starting soon after radiotherapy to promote increased vascularisation of the muscles by forming collateral vessels. Prospective studies are needed to assess the effectiveness of such programs.

Future perspectives and cardiovascular screening programs

Extrapolating the findings in our studies the following screening recommendations for cardiovascular disease seem reasonable (Figure):

1. At HL diagnosis patients older than 35 years should be screened for cardiovascular risk factors and cardiovascular burden in order to suggest a patient tailored HL therapy. We recommend considering treatment with only chemotherapy in the following situations:
    - patients with a previous history of CAD or stroke/transient ischemic attacks.
    - patients above 35-40 years and:
        - o two or more cardiovascular risk factors or
        - o high cardiovascular risk based on additional screening tests. Screening tests can consist of arterial stiffness parameters (PWV/DC) and perhaps also atherosclerotic measurements (CAC score/IMT).

2. After HL treatment including mediastinal radiotherapy screening for CAD should be performed as follows:
   - HL patients with a low risk for CAD (age at treatment < 35 years, 0-1 cardiovascular risk factors, radiotherapy dose < 36Gy to the mediastinum) should undergo screening for CAD by CAC-score at 10 years after mediastinal radiotherapy.
   - HL with a high risk for CAD should undergo screening for CAD 5 years after mediastinal radiotherapy
   - In HLS with significantly increased CAC-scores, additional ischemia-detection tests or coronary artery imaging should be considered.
   - Subsequent screening points should be scheduled depending on the abnormalities observed at first screening, on the complaints of the patient and on the cardiovascular risk profile.

3. After HL treatment including radiotherapy to the neck, HLS should be screened by Doppler ultrasound of the neck arteries at 15 years after radiotherapy:
   - If plaque is present in the neck arteries, HLS should be monitored more often by their treating neurologist for the timely detection of significant stenoses. Sequential IMT measurements is probably not of prognostic significance, as has been demonstrated recently[36], therefore we do not recommend following IMT.
   - Aggressive medical treatment should be considered even in the absence of asymptomatic stenoses in patients with (quickly developing) atherosclerosis of the neck arteries.
   - If a significant stenosis has occurred, patients tailored therapy should be instituted as advised by current guidelines[19], considering aggressive medical therapy, percutaneous carotid stenting or surgical interventions.

4. After treatment including radiotherapy to the mediastinum, HLS:
   - should undergo a screening echocardiography (and possibly also an ECG) 10 years after mediastinal radiotherapy for the timely detection of valvular disorders and functional cardiac problems.

- These screening modalities should be repeated at an interval dependent on the detected abnormalities. If no disorders are found at screening 10 years after mediastinal radiotherapy, HLS should not be discharged from follow-up, but a next screening moment should be scheduled probably 5-10 years after the first echocardiogram.

5. After treatment with anthracycline containing chemotherapy cardiac function should be assessed as well.[37] In this study we did not focus on HLS treated with anthracycline chemotherapy.

In conclusion, we have updated our earlier recommendations made in **chapter 2** (based on the literature reviewed at that time) with the data from the current studies (Figure). The most important change is lowering the age at which decision making regarding the most appropriate treatment for HL patients should be made, taking into consideration the individual CV risk profile. Based on the literature review we previously recommended 45 years, but based on results from **chapter 3** we recommend regarding HL patients aged 35-40 as being already at risk of developing CVD after treatment with radiotherapy. We also recommend screening for sub-clinical cardiovascular disease (arterial stiffening and perhaps atherosclerosis) and cardiovascular risk factors at the moment of HL diagnosis. Furthermore, we added the suggestion of screening HLS treated with radiotherapy to the neck with Doppler ultrasound of the cervical arteries starting 15 years after radiotherapy.
Further studies should be performed in recently treated HLS to confirm these recommendations, especially for HL patients treated with lower radiotherapy doses of 20-30 Gy. Recommendations based on this group of HLS should be evaluated for the individual HLS. The cohort of HLS described in this thesis should be followed five years after these screening studies in order to determine which of the screening modalities have the strongest predictive power for cardiovascular and neurological disease.

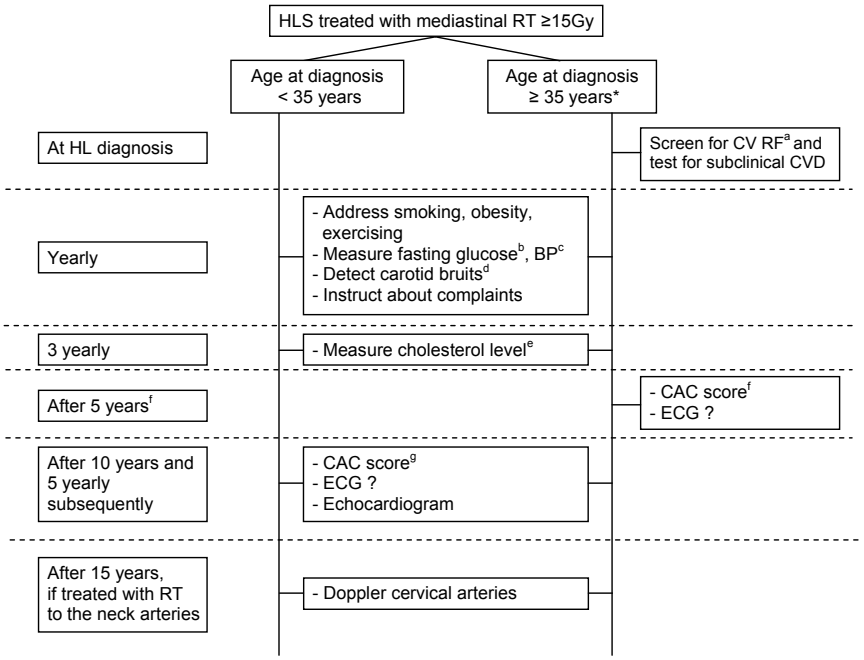


Figure: Cardiovascular screening program in HLS.
BP blood pressure; CAC coronary artery calcium; CVD cardiovascular disease; ECG electrocardiogram; HLS Hodgkin lymphoma survivors; RF risk factor; RT radiotherapy.

* Consider treating HL patients aged > 35 years at diagnosis without radiotherapy in case of a prior history of CVD, if having ≥ 2 RF for CVD at HL diagnosis or if having a high CV risk profile after screening with arterial stiffness parameters (PWV/DC) and perhaps atherosclerotic parameters (IMT/CAC-score).

a Cardiovascular RF: hypercholesterolemia, hypertension, obesity, smoking, positive family history of cardiovascular disorders, history of cardiovascular disorders. In case of previous cardiovascular disease or a high risk profile (including cardiovascular complaints), consider treating HL without RT to the mediastinum.
b Treat diabetes mellitus according to the ADA/EASD guidelines44, considering RT as one risk factor for atherosclerosis.
c Treat hypertension according to the JNC 7 guidelines45, considering RT as one risk factor for atherosclerosis.
d In HLS treated by cervical RT.
e Treat hypercholesterolemia according to the NCEP ATP III guidelines46, considering RT as a risk factor.
f Also perform measurements of CAC score after 5 years in HLS <35 years at diagnosis with ≥ 2 RF for cardiovascular disease.
g In case of a CAC-score >0 referral to a cardiologist for ischemia detection. If no ischemia is detected on additional testing and there are no cardiac symptoms, repeat CAC-score in 5 years. In case of an augmentation of the CAC-score during subsequent testing, ischemia detection should be repeated as well.

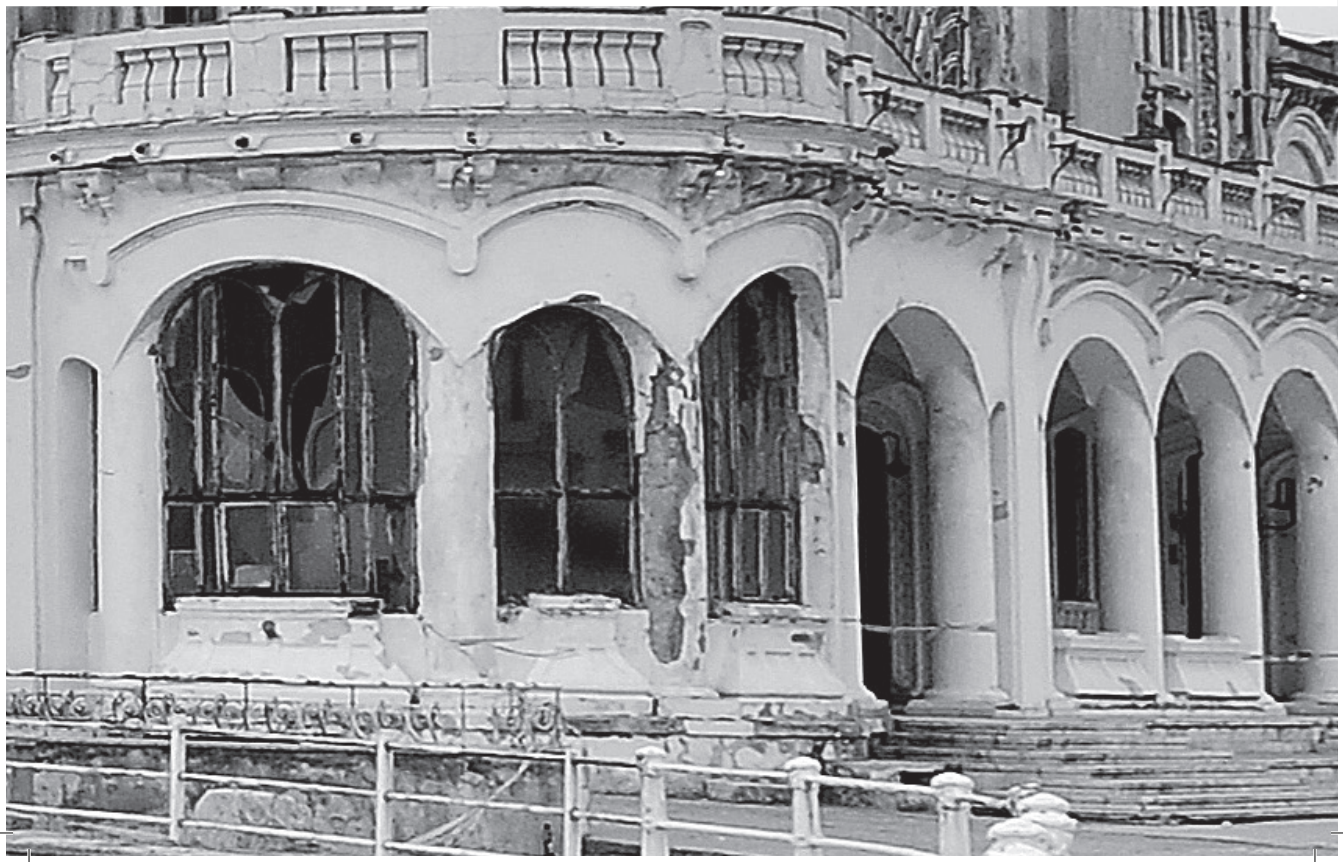
References

1. Aleman BM. Optimizing treatment of patients with Hodgkin's lymphoma. Faculty of Medicine. Academic Medical Center, University of Amsterdam; 2007, ISBN 9090215018 ; 9789090215013.
2. Ferme C, Eghbali H, Meerwaldt JH*, et al.* Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med* 2007;357:1916-1927.
3. Zelcer S, Chen B, Mangel J*, et al.* Impaired vascular function in asymptomatic young adult survivors of Hodgkin Lymphoma following mediastinal radiation. *J Cancer Surviv* 2010;4:218-224.
4. Sugihara T, Hattori Y, Yamamoto Y*, et al.* Preferential impairment of nitric oxide-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. *Circulation* 1999;100:635-641.
5. Beckman JA, Thakore A, Kalinowski BH*, et al.* Radiation therapy impairs endothelium-dependent vasodilation in humans. *J Am Coll Cardiol* 2001;37:761-765.
6. Brosius FC, 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981;70:519-530.
7. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. *Catheter Cardiovasc Interv* 2008;72:563-568.
8. Russell NS, Hoving S, Heeneman S*, et al.* Novel insights into pathological changes in muscular arteries of radiotherapy patients. *Radiother Oncol* 2009;92:477-483.
9. Lyons D, Roy S, Patel M*, et al.* Impaired nitric oxide-mediated vasodilatation and total body nitric oxide production in healthy old age. *Clin Sci (Lond)* 1997;93:519-525.
10. Stewart FA, Heeneman S, Te Poele J*, et al.* Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am J Pathol* 2006;168:649-658.
11. Karalliedde J, Smith A, DeAngelis L*, et al.* Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 2008;51:1617-1623.
12. van Leeuwen-Segarceanu EM, Tromp WF, Bos WJ*, et al.* Comparison of two instruments measuring carotid-femoral pulse wave velocity: Vicorder versus SphygmoCor. *J Hypertens* 2010;28:1687-1691.
13. Wilkinson IB, Fuchs SA, Jansen IM*, et al.* Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998;16:2079-2084.
14. Aleman BM, van den Belt-Dusebout AW, De Bruin ML*, et al.* Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109:1878-1886.

15. 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;99:206-214.
16. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol* 1993;11:1208-1215.
17. Glanzmann C, Kaufmann P, Jenni R*, et al.* Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol* 1998;46:51-62.
18. Hull MC, Morris CG, Pepine CJ*, et al.* Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *Jama* 2003;290:2831-2837.
19. Goldstein LB, Bushnell CD, Adams RJ*, et al.* Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:517-584.
20. Ricotta JJ, Aburahma A, Ascher E*, et al.* Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *J Vasc Surg* 2011;54:832-836.
21. Fokkema M, den Hartog AG, Bots ML*, et al.* Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. *Stroke* 2012;43:793-801.
22. Fokkema M, den Hartog AG, van Lammeren GW*, et al.* Radiation-induced carotid stenotic lesions have a more stable phenotype than de novo atherosclerotic plaques. *Eur J Vasc Endovasc Surg* 2012;43:643-648.
23. Arad Y, Spadaro LA, Roth M*, et al.* Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005;46:166-172.
24. Raggi P, Davidson M, Callister TQ*, et al.* Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* 2005;112:563-571.
25. Schmermund A, Achenbach S, Budde T*, et al.* Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. *Circulation* 2006;113:427-437.
26. Haberl R, Becker A, Leber A*, et al.* Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001;37:451-457.
27. King V, Constine LS, Clark D*, et al.* Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1996;36:881-889.

28. Dijk JM, van der Graaf Y, Bots ML, *et al.* Carotid intima-media thickness and the risk of new vascular events in patients with manifest atherosclerotic disease: the SMART study. *Eur Heart J* 2006;27:1971-1978.
29. Dijk JM, van der Graaf Y, Grobbee DE, *et al.* Increased arterial stiffness is independently related to cerebrovascular disease and aneurysms of the abdominal aorta: the Second Manifestations of Arterial Disease (SMART) Study. *Stroke* 2004;35:1642-1646.
30. Meyer RM, Hoppe RT. Point/counterpoint: early-stage Hodgkin lymphoma and the role of radiation therapy. *Blood* 2012;120:4488-4495.
31. 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;22:3139-3148.
32. Heidenreich PA, Hancock SL, Lee BK, *et al.* Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 2003;42:743-749.
33. Wethal T, Lund MB, Edvardsen T, *et al.* Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. *Br J Cancer* 2009;101:575-581.
34. Gottdiener JS, Katin MJ, Borer JS, *et al.* Late cardiac effects of therapeutic mediastinal irradiation. Assessment by echocardiography and radionuclide angiography. *N Engl J Med* 1983;308:569-572.
35. Pohjola-Sintonen S, Totterman KJ, Salmo M, *et al.* Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. *Cancer* 1987;60:31-37.
36. Lorenz MW, Polak JF, Kavousi M, *et al.* Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012;379:2053-2062.
37. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, 2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

11 Nederlandse samenvatting



Introductie

Hodgkin lymfoom is een vorm van lymfklierkanker die in Nederland jaarlijks bij ongeveer 400 patiënten wordt vastgesteld. Bij diagnose zijn de patiënten meestal tussen de 20 en 35 jaar oud of ouder dan 50 jaar. De laatste decennia zijn de mogelijkheden voor behandeling aanzienlijk verbeterd, waardoor tegenwoordig ongeveer 80-90% van de patiënten geneest. De kans op een recidief van het Hodgkin lymfoom is vanaf 10 jaar na diagnose erg klein. Daarentegen, neemt de kans op complicaties gerelateerd aan de behandeling juist toe in de loop der jaren.

De behandeling van het Hodgkin lymfoom bestaat uit chemotherapie met of zonder bestraling, afhankelijk van het stadium waarin de ziekte zich bevindt. Patiënten met stadium I of II (ziekte beperkt zich tot één lymfkliergebied/orgaan of twee of meer lymfkliergebieden boven of onder het middenrif) worden behandeld met chemotherapie, meestal gevolgd door bestraling. Patiënten met meer verspreide ziekte (stadium III of IV) ontvangen veelal alleen chemotherapie (intensiever of meer cycli dan bij stadium I of II). Aanvullende bestraling vindt alleen nog plaats als de ziekte niet geheel op de chemokuren heeft gereageerd.

Vroeger werd bestraling ook zonder chemotherapie toegepast en was het bestralingsgebied vaak uitgebreider (niet alleen de aangedane lymfklieren, maar ook de aangrenzende lymfklierstations werden bestraald; bijvoorbeeld de mantelveldbestraling). Hierdoor vielen ook grote delen van gezond weefsel (zoals hart, longen, borsten) in het bestralingsgebied. Om de schade aan de gezonde weefsels te beperken, werd in de loop van de jaren het bestralingsgebied kleiner (alleen de betrokken lymfklierstations of zelfs alleen de betrokken lymfklieren werden bestraald); de totale dosis bestraling werd ook verminderd, van 40Gy naar 20-30Gy. Door bestraling te combineren met chemotherapie (ook aangepast omdat sommige middelen meer kans op een secundaire leukemie gaven) was kans op genezing van de patiënten nog steeds groot, met minder kans op lange termijn complicaties.

De meeste lange termijn complicaties worden veroorzaakt door bestraling. Daarom wordt tegenwoordig onderzocht of bestraling helemaal achterwege gelaten kan worden bij bepaalde groepen Hodgkin patiënten die goed reageren op de chemokuren. Ook wordt

onderzocht welke combinatie van chemokuren de beste kans op genezing geeft met de daarbij de kleinste kans op bijwerkingen.
De meest voorkomende late effecten van bestraling zijn het ontwikkelen van nieuwe kwaadaardige ziekten uitgaande van weefsels in het bestralingsveld (bv. borstkanker of longkanker). Daarnaast blijkt dat hart- en vaatziekten frequent voorkomen als doodsoorzaak bij Hodgkin patiënten (de tweede doodsoorzaak na kwaadaardige ziekten). Eerdere onderzoeken naar het hart- en vaatziekten bij Hodgkinpatiënten richtten zich op symptomatische patiënten. Er zijn maar weinig studies naar het voorkomen van beginnende (asymptomatische) hart- en vaatziekten lange tijd na behandeling voor Hodgkin lymfoom. Het is daarom ook niet bekend welke tests men het beste kan inzetten om asymptomatische hart- en vaatziekten op te sporen.

Inhoud proefschrift

In een dwarsdoorsnede (cross-sectioneel) onderzoek is in dit proefschrift het voorkomen van asymptomatische hart- en vaatziekten onderzocht bij 82 patiënten die succesvol zijn behandeld voor Hodgkin lymfoom en bij 40 gezonde vrijwilligers. Verschillende indicatoren van vroege hart- en vaatziekten zijn gemeten. Tevens is gezocht naar Hodgkin therapie- en patiënt gerelateerde risicofactoren die voorspellers kunnen zijn voor het optreden van hart- en vaatziekte op de lange termijn. Daarnaast wordt aandacht besteed aan minder bekende complicaties bij Hodgkin patienten, namelijk neurologische problemen van het nek- en schoudergebied. Dit proefschrift beoogt te komen tot een screeningsprogramma voor Hodgkin patiënten om hart- en vaatziekten in een vroege fase op te sporen.
In **hoofdstuk 2** wordt een overzicht gegeven van de beschikbare literatuur over cardiovasculaire complicaties van bestraling. Vervolgens wordt een suggestie gegeven voor een cardiovasculair screeningsprogramma voor Hodgkin patiënten, gebaseerd op de weergegeven studies. Screening op kransslagader afwijkingen wordt aanbevolen vanaf 5 jaar na bestraling op de thorax bij Hodgkin patiënten van 45 jaar of ouder (op het moment van bestraling) en bij jongere patiënten met twee of meer risicofactoren voor hart- en vaatziekten. Bij de overige patiënten kan de screening met CAC-score beginnen vanaf 10 jaar na bestraling op de thorax. Tien jaar na

bestraling is bij alle patiënten ook een screenings-echocardiografie aanbevelenswaardig om hartklepafwijkingen op te sporen. Om hartritmestoornissen te detecteren zou een ECG moeten plaatsvinden bij klachten of bij elk cardiovasculair screeningsmoment. Traditionele risicofactoren voor hart- en vaatziekte zullen zeker behandeld moeten worden. Behandelende artsen zullen zich bewust moeten zijn van de verhoogde risico's op hart- en vaatziekten bij Hodgkin patiënten. Ook zullen patiënten instructies moeten ontvangen, wanneer (bij welke klachten) zij zich bij een arts moeten melden.
Bij andere patiëntengroepen met een verhoogd risico op hart- en vaatziekten (zoals patiënten met diabetes, nierziekten, hypertensie) zijn meer onderzoeken verricht naar de waarde van screeningstesten. Een aantal indicatoren voor vaatstijfheid van slagaders voorspelt bij deze patiënten het optreden van hartinfarcten en herseninfarcten. In **hoofdstuk 3** worden twee van deze parameters onderzocht: de pols golf snelheid (PWV) over de aorta en de distensibiliteitscoëfficient (DC) van de halsslagaders bij Hodgkin patiënten en vrijwilligers. Hoge PWV en lage DC geven stijvere slagaders aan. De PWV was hoger bij patiënten bestraald op oudere leeftijd (40 jaar of ouder) in vergelijking met patiënten bestraald op jongere leeftijd, patiënten behandeld met alleen chemotherapie of vrijwilligers. Vergelijkbare resultaten werden gevonden voor de DC. De laagste DC werd gevonden bij patiënten bestraald op 35 jarige leeftijd of ouder. Dit is de eerste publicatie over vaatstijfheidsparameters na bestraling.
In **hoofdstuk 4** worden twee apparaten vergeleken voor de meting van PWV in gezonde vrijwilligers. Er is geen consensus over de wijze waarop de PWV het beste kan worden vastgelegd, waardoor nu verschillende methoden worden gebruikt. De nieuwe Vicorder blijkt minder goede diagnostische eigenschappen te hebben dan de SphygmoCor (die langer in gebruik is). In het vervolgonderzoek in hoofdstuk 3 gebruiken we de SphygmoCor.
In de loop van de jaren is bekend geworden dat patiënten die bestraald zijn geweest een hogere kans hebben op het ontwikkelen van een herseninfarct. Eén van de verklaringen is dat bestraling aderverkalking kan veroorzaken. Het vroeg opsporen van aderverkalking in de halsslagaders kan plaatsvinden door het meten van de Intima-Media Thickness (IMT). De IMT is de dikte van de binnenste twee lagen (intima

en media) van de wand van een slagader en wordt vooral bepaald door de mate van aderverkalking. Een hogere IMT, samen met het voorkomen van de atherosclerotische plaque (die zich in een latere fase vormt), zijn sterke voorspellers van een herseninfarct. In **hoofdstuk 5** worden de resultaten van de IMT metingen en het voorkomen van plaques in de halsslagaders vergeleken tussen Hodgkin patiënten die wel/niet bestraald zijn op de hals en vrijwilligers. Bestraling op de hals van meer dan 15 jaar geleden was geassocieerd met het de hoogste IMT en het optreden van plaques. Daarnaast waren leeftijd, buikomvang en roken geassocieerd met een hogere IMT.

Hodgkin patiënten die bestraald zijn op de thorax hebben een verhoogd risico op het krijgen van een hartinfarct. Dit is meestal het gevolg van kransslagadervernauwing als gevolg van aderverkalking. Verkalkingen in de kransslagaders kunnen in een vroege fase opgespoord worden met CT-scans die coronaire calcium scores (CAC-scores) berekenen. Een CAC-score boven het 75ste percentiel voor leeftijd en geslacht is geassocieerd met een verhoogd risico op het krijgen van een hartinfarct. In **hoofdstuk 6** worden de resultaten van CAC-score metingen beschreven. Iets meer dan de helft van Hodgkin patiënten die bestraald waren op de thorax meer dan 10 jaar geleden had een CAC score boven het 75ste percentiel, in vergelijking met ongeveer 10% van de niet bestraalde patiënten en patiënten die korter geleden bestraald waren. Er waren meer traditionele risicofactoren (diabetes, hoge bloeddruk, roken etc.) aanwezig in de patiënten met een significant verhoogde CAC score.

In **hoofdstuk 7** worden hartklepafwijkingen beschreven bij de Hodgkin patiënten. Patiënten die bestraald waren op de thorax hadden vaker hartklepafwijkingen. De meest vaak voorkomende klepafwijkingen waren aortaklepinsufficiëntie en mitralisklepinsufficiëntie. Hoge bloeddruk en een langere tijd na bestraling waren geassocieerd met deze klepafwijkingen in bestraalde patiënten. Van de bestraalde patiënten, had 14% een hartklepoperatie ondergaan; hartklepchirurgie kwam in het geheel niet voor in de niet-bestraalde groep.

Tijdens het screeningsprogramma viel op dat veel Hodgkin patiënten klachten hadden van zwakte en pijn van de nekspieren. Twaalf Hodgkin patiënten die behandeld waren met de mantelveldbestraling werden uitgebreider onderzocht om de oorzaak van deze klachten

te achterhalen. De resultaten van deze aanvullende tests worden beschreven in **hoofdstuk 8.** De nekbuigers bleken vaker aangedaan te zijn dan de nekstrekkers. De schade aan de spieren die in het bestralingsveld lagen bleek veroorzaakt te zijn door directe schade aan de spieren zelf, terwijl de schade aan de spieren die net buiten het bestralingsveld lagen veroorzaakt was door schade aan de zenuwen. De uitslagen van de verschillende onderzoeken wijzen erop dat deze spier- en zenuwschade waarschijnlijk veroorzaakt werd door het effect van de bestraling op de bloedvaten in de spieren en de zenuwen. Deze bevindingen betekenen dat patiënten die radiotherapie hebben ondergaan op de nek waarschijnlijk baat hebben bij spierversterkende oefeningen indien er klachten optreden van de nekspieren.

Voorstel voor een screeningsprogramma voor het opsporen van hart- en vaatziekten bij Hodgkin patiënten

Op basis van de bovengenoemde bevindingen en de beschikbare literatuur kunnen de volgende adviezen gegeven worden:

1. Bij diagnose moeten Hodgkin lymfoom patiënten ouder dan 35 jaar gescreend worden op risicofactoren voor hart- en vaatziekten en op reeds aanwezige cardiovasculaire schade. Overweeg het weglaten van bestraling als onderdeel van de behandeling bij:
    - patiënten met hart- of vaatziekten in de voorgeschiedenis.
    - patiënten ouder dan 35-40 jaar met:
        - twee of meer traditionele risicofactoren voor hart- en vaatziekte
        - verhoogd cardiovasculair risico op basis van aanvullende screeningstesten (vaatstijfheid, coronair-calcium-score)

2. Bij Hodgkin lymfoom patiënten die op de thorax bestraald zijn geweest, wordt de volgende screening voor schade aan de kransslagaders geadviseerd:
    - screen patiënten met een laag cardiovasculair risico (leeftijd bij behandeling < 35 jaar, 0-1 cardiovasculaire risicofactoren, bestralingsdosis < 36 Gy op de thorax) met een CAC-score vanaf 10 jaar na bestraling

- screen patiënten met een hoog cardiovasculair risico met een CAC-score vanaf 5 jaar na bestraling
- overweeg aanvullende ischemie-detectie testen in asymptomatische Hodgkin patiënten met een significant verhoogde CAC-score
- het interval van vervolgscreening na de initiële CAC-score meting zou bepaald moeten worden op basis van de afwijkingen bij de eerste test, klachten en cardiovasculaire profiel

3. Bij Hodgkin lymfoom patiënten die bestraald geweest zijn op de nek, wordt screening op schade aan de halsslagaders geadviseerd vanaf 15 jaar na bestraling:
   - als plaques worden gevonden in de halsslagaders, moeten patiënten nauwkeurig vervolgd worden door de neuroloog om tijdig significante vernauwing op te sporen.
   - intensieve medicamenteuze behandeling (met bv. cholesterolverlagers, bloedverdunners) wordt aanbevolen indien snel ontwikkelende atherosclerose van de slagaders wordt gevonden.
   - bij significante vernauwingen in de halsslagaders moet de behandeling (operatie van de halsslagaders of stentplaatsing) aangepast worden op de individuele patiënt.

4. Hodgkin lymfoom patiënten die bestraald zijn geweest op de thorax:
   - zouden een screenings echocardiografie moeten ondergaan 10 jaar na bestraling, om hartklepafwijkingen op te sporen
   - op basis van de bevindingen bij de eerste echocardiografie moet het interval bepaald worden voor vervolgonderzoek. In elk geval moeten patiënten niet uit de controle ontslagen worden, maar moet er een echocardiografie herhaald worden na 5-10 jaar.

11 Dankwoord

Allereerst wil ik alle Hodgkin patiënten en hun partners bedanken voor deelname aan dit onderzoek. Zonder u was dit onderzoek er niet geweest.

Prof. dr. D.H. Biesma, beste Douwe. Mijn eerste contact met de hematologie was als derdejaars co-assistent op de D2 in het St. Antonius. Ik kan me nog steeds de grote visite herinneren met jou, Okke en Gerda met papieren dossiers op de kamer van de hoofdverpleegkundige, inclusief lastige vragen voor de co-assistent. Wat is er sindsdien veel gebeurd en wat heb ik veel aan jou te danken! Na mijn semi-arts stage bij de hematologie mocht ik in het St. Antonius blijven werken als AGNIO. Het leek me ook leerzaam om onderzoek te doen en toen stelde je voor dat ik het onderzoeksplan over late complicaties bij Hodgkin patiënten kon oppakken. Zelf had ik toen nog niet het idee dat dit tot een opleidingsplek bij de Interne Geneeskunde en een promotie zou leiden, maar jij had natuurlijk al een plan bedacht. Dit is typerend voor de rest van onze samenwerking. Door je vooruitziende blik en faciliterend en organisatorisch talent was het mogelijk om dit onderzoek op te zetten en mij in de gelegenheid te stellen te promoveren. Ook al was het niet altijd eenvoudig om onderzoek te combineren met alle andere gebeurtenissen in mijn leven, ik ben heel blij dat ik het gedaan heb en ik ben je heel dankbaar voor je altijd bemoedigende woorden in tijden dat de vaart er niet meer zo in zat.

Dr. O.J.M. Vogels, beste Oscar. Wat begon als een idee van jou en Lucille om de IMT te meten bij bestraalde patiënten, is uitgegroeid tot een heel screeningsprogramma. Je stond altijd open voor nieuwe ideeën en motiveerde iedereen op de KNF om aan ons onderzoek mee te werken. Ik heb veel bewondering voor hoe deskundig en nauwkeurig je het neurologische onderzoek uitvoerde en tegelijkertijd veel aandacht had voor het persoonlijke verhaal van de deelnemers. Je kende uiteindelijk het persoonlijke verhaal van bijna alle patiënten. Je merkte terecht op dat het een bijzondere groep patiënten is die veel heeft meegemaakt, maar ondanks klachten of lange termijn effecten van de behandeling heel sterk en gemotiveerd in het leven staat. Bedankt voor de vele leerzame uren op de KNF! Of het nu Duplex uitslagen, plaques of nekspieren betrof, je nam altijd rustig de tijd om mijn vragen te beantwoorden.

Dr. W.J.W. Bos, beste Willem-Jan. Je was niet vanaf het begin bij het onderzoek betrokken, maar tijdens een onderzoeksbespreking met Douwe, Oscar en Lucille ontstond het idee om vaatstijfheidsmetingen toe te voegen aan het onderzoeksprotocol. Je kwam even tijdens je drukke programma op de kamer van Oscar en je was gelijk enthousiast. Uiteindelijk heb je als vaatspecialist veel bijgedragen aan het gehele onderzoek. Wat heb jij veel tijd besteed aan het nakijken van mijn manuscripten! Als je even tijd had, in de trein of het vliegtuig (ik geloof dat er ergens nog op een vliegveld een eerste versie van een manuscript ligt), keek je alle stukken aandachtig na. Zelfs op de racefiets of in de skilift werden er nog korte onderzoeksbesprekingen gehouden. Bedankt voor je goede begeleiding met aandacht voor zowel de persoonlijke als de professionele zaken.

Dr. L.D.A. Dorresteijn, beste Lucille. Het bestuderen van vaatschade na bestraling bij Hodgkin patiënten werd door jou voorgesteld in het kader van je promotie onderzoek. Inmiddels ben je zelf gepromoveerd en heeft dit onderzoek geen onderdeel uitgemaakt van jouw boekje, maar je hebt er onzettend veel werk ingestoken om het te kunnen initiëren. Jouw ervaring in het NKI-AvL en Nijmegen en grote inhoudelijke kennis zijn heel belangrijk geweest bij het opzetten van het onderzoek. Je waardevolle praktische adviezen, bijvoorbeeld over het zelf volgen van een goede statistiekcursus vroeg in het beloop van het onderzoek, hebben me veel geholpen. Ik kijk met plezier terug op de uren die we bij je thuis hebben doorgebracht bij het opzetten van de database in Access (met de vrolijke afleiding van de net geboren Nanne) en later de besprekingen over de nekspieren. Jammer dat Enschede zo ver weg is, want bij elkaar zitten was heel gezellig!

De fijne samenwerking voor dit onderzoek met de afdeling cardiologie en radiologie is kenmerkend voor de prettige, collegiale sfeer in het St. Antonius ziekenhuis. Dr. Benno Rensing en Dr. Jan van der Heijden, hartelijk dank voor jullie betrokkenheid bij dit project. Jullie waren altijd bereid mee te denken over welke screeningsmethoden we het beste konden gebruiken en leverden kritisch commentaar op de manuscripten. Dr. Marco Post en drs. Jesse Bijl, hartelijk dank voor het beoordelen van de echocardiografiebeelden en het analyseren van de verkregen data. Marleen Roos, student geneeskunde, maar inmiddels zelf arts, dank voor je hulp bij de dataverwerking en bij het schrijven van het artikel over de hartkleppen.

De leden van de leescommissie prof. dr. M.L. Bots, prof. dr. M.H.H. Kramer, prof. dr. ir. F. E. van Leeuwen, prof. dr. M.C. Verhaar, en prof. dr. J.H.J. Wokke wil ik graag bedanken voor hun kritische beoordeling van het manuscript.

De samenwerking met de AMC-groep van dr. Jaap Groothoff op het gebied van PWV meetmethodes heeft geleid tot de eerste publicatie van dit project. Ik wil dan ook dr. Hanneke van der Lee speciaal bedanken voor het begeleiden van mijn eerste publicatie. De werelden van SPSS en submissions werden een stuk eenvoudiger na jouw tips en tricks.

Dr. Nens van Alfen en de afdeling klinische neurofysiologie van het UMC St. Radboud ziekenhuis in Nijmegen wil ik bedanken voor het beschikbaar stellen van hun middelen en grote expertise om de nekschade na mantelveld radiotherapie nader te onderzoeken. Nens, jouw kennis op dit gebied is indrukwekkend en de doortastende manier van onderzoeken zijn zeer belangrijk geweest voor de resultaten van onze zoektocht naar de oorzaak van de nekklachten. Bovendien was jouw prettige begeleiding bij het schrijven van het artikel heel leerzaam, zeker voor mij als hematoloog in wording met veel belangstelling, maar weinig verstand van de neurofysiologie.

Danny van Maurik, altijd vrolijk en opgewekt, vol met verhalen over je mooie reizen. Als je aan het werk was, was je altijd secuur en betrouwbaar. Je hebt veel vrije tijd besteed op de KNF afdeling om de Hodgkin patiënten en de gezonde deelnemers te onderzoeken. Het was nooit een probleem wanneer een deelnemer liever na zijn werk, in de avonduren wilde komen. Je vond het ook leuk om nieuwe dingen te leren, dus de nieuwe technieken van het meten van de PWV had je zo onder de knie. Het was leuk om met je samen te werken, dank je wel voor je inzet voor de Hodgkin patiënten.

De verschillende afdelingen van het St. Antonius ziekenhuis wil ik bedanken voor het begeleiden van de deelnemers aan dit onderzoek. In het bijzonder wil ik Willeke van de KNF afdeling, Loes van de hartfunctie afdeling en de verschillende medewerkers van de radiologie afdeling bedanken voor hun hulp. De afdeling Research en Development van de Maatschap Interne en met name Nicole en Irma; fijn dat jullie mij zo konden steunen met de METC aanvragen en later het afnemen van

de vragenlijsten bij de deelnemers. Ook Joke, Marianne en Irene, dank voor jullie belangstelling en ondersteuning bij alle logistiek rond mijn opleiding en onderzoek.

De maatschap Interne Geneeskunde van het St. Antonius ziekenhuis en mijn collega's arts-assistenten wil ik bedanken voor hun belangstelling tijdens mijn promotie onderzoek. Dr. Tom Geers in het bijzonder dank voor je toestemming om twee keer mijn opleiding te onderbreken voor onderzoek. Door die onderbrekingen heb ik een extra lange opleidingstijd in Nieuwegein gehad en het voelt nog steeds als thuis als ik terug ben; het kost nog steeds moeite om in het UMC een zin niet te beginnen met 'wij in Nieuwegein…'. Dr. Mariette Agterof, fijn dat ik gebruik mocht maken van de door jou verzamelde gegevens over de Hodgkin populatie. Je promoveerde op de HOME studie, maar de uren die je gestoken hebt in dit onderzoek zijn ook zeker zeer waardevol geweest. Ook de hematologen van het St. Antonius ziekenhuis wil ik bedanken voor het motiveren van de patiënten om mee te doen aan dit onderzoek en voor de begeleiding tijdens mijn periodes op de hematologie afdeling.

De hematologen van het UMC Utrecht en mijn collega fellows en assistenten bedankt voor jullie belangstelling en het invallen tijdens de afrondende maand van mijn onderzoek. Dr. Reinier Raymakers, fijn dat ik die extra tijd onderzoeksverlof mocht opnemen om de promotie af te ronden.

Sabine en Doreen, paranimfen hoeven tegenwoordig geen vragen meer te beantwoorden van de commissie, maar volgens mij horen ze met name goed te weten wat een promovendus allemaal heeft meegemaakt tijdens de promotietijd. Jullie hebben mij de afgelopen jaren veel gesteund en jullie belangstelling en tips hebben me veel geholpen. We hebben uiteindelijk allemaal verschillende paden bewandeld tot de doctorstitel (Doreen, bij jou is het einde ook in zicht), maar we hebben toch wel heel veel dingen gemeen: met onderzoek (en opleiding) beginnen in het Antonius, nagenoeg dezelfde onderzoeksbegeleiders en daarbij ook nog kinderen krijgen en trouwen (en allemaal niet per sé volgens de ideale volgorde van Douwe). Lieve Sabine, jouw doorzettingsvermogen en geconcentreerde en enthousiaste manier van werken zijn enorm inspirerend en werken aanstekelijk. Ik heb

onzettend veel bewondering voor je en vind het heel fijn dat je er altijd bent, bij leuke dingen maar ook in minder leuke tijden. Ik kijk er naar uit om straks samen achter onze vier mannetjes te rennen, maar ook weer eens samen te skiën. Lieve Doreen, wat hebben we samen veel gelachen, op de racefiets, tijdens de EHA congressen, op je bruiloft. Jij bent altijd zo enorm vrolijk en ongecompliceerd dat het altijd gezellig is als je er bent. Snel promoveren daar in Amsterdam en dan kunnen we zonder zorgen weer leuke dingen doen samen en dan een leuke hematologie kliniek samen beginnen!

Lieve oma en grootvader Stoop, zonder uw in mij gestelde vertrouwen en uw motiverende woorden op de juiste momenten zou ik hier vandaag niet staan! Ik weet zeker dat grootvader tevreden naar beneden kijkt nu; dit proefschrift wil ik dan ook graag aan u beiden opdragen. Bedankt dat ik uw kleindochter mag zijn!

Lieve Roel, Diny, Esther, Ruben en Eva. Jullie hebben mij de laatste jaren laten ervaren hoe belangrijk het is om een warme, vertrouwde, liefdevolle thuisbasis te hebben, helemaal als je ver van huis bent. Jullie zijn mijn Nederlandse familie en zonder jullie had ik me nooit zo thuis gevoeld in Nederland en het nooit volgehouden in moeilijke momenten. Door jullie onvoorwaardelijke steun heb ik kunnen doen wat ik graag doe en kunnen zijn wie ik ben en dat heeft me zover gebracht. Bedankt!

Lieve schoonfamilie, toen ik dit dankwoord begon te schrijven had ik nooit gedacht dat mijn lieve schoonmoeder er plotseling niet meer zou zijn als ik mijn proefschrift af had. Ik zou schrijven: Annie en Ben, zonder jullie oppashulp op mijn 'mamadag' had ik dit boek nooit kunnen afmaken. Wetende dat Tim in zulke goede handen was heeft me altijd de rust gegeven om het proefschrift af te maken. Annie, je zult altijd in onze gedachten blijven, dit boek is nu voor jou.

Dragă mama si dragă Ioana, vă mulţumesc ca m-aţi ajutat totdeauna in momentele grele şi că aţi fost alături de mine in momentele fericite. Nu o să uit niciodată originile noastre şi nici faptul că şi datorita voua am reuşit in viaţa. Simbol al rădăcinilor noastre şi ale lui Maia si Tau, am ales Cazinoul pe copertă, super mulţumesc Ioana!

Allerliefste Bernie, er zijn niet genoeg woorden om te omschrijven hoe onzettend dankbaar ik ben voor je hulp de afgelopen jaren. Ik ben zo gelukkig bij jou, je steunt me in alles en we passen het beste bij elkaar! Ik houd van jou het allermeeste. We gaan met onze jongens nog mooie avonturen meemaken!

Tim, lieve, kleine boef en grote jongen, mama komt nu met jou spelen, de laptop gaat dicht... tenzij je Bumba, Pieter Post, Woezel & Pip of Shrek wil kijken! Nu hoeft mama niet meer bang te zijn dat je de laatste versie van het manuscript per ongeluk gaat deleten.

11 Curriculum vitae

Elena Monica Segărceanu werd geboren op 24 mei 1980 in Constanţa, Roemenië. Tijdens haar jeugd heeft ze veel tijd doorgebracht bij haar grootouders in Constanţa, aan de Zwarte Zee. Vervolgens heeft ze het basisonderwijs gevolgd in Boekarest. Op haar 12e jaar verhuisde ze voor een half jaar met haar moeder en zusje naar Nederland, op uitnodiging van de Jan en Pauline Stoop. Ze volgde in die periode basisonderwijs op de Daltonschool Pieterskerkhof in Utrecht, waar ze Nederlands leerde. Na terugkeer in Roemenië bezocht ze de middelbare school, het Cantemir Voda College in Boekarest, tot en met 5 VWO. In 1998 kwam ze naar Nederland in het kader van een internationaal uitwisselingsjaar van de Rotary Club in Dronten, door bemiddeling van Lammert en Anneke Segaar. Na een verblijf van een jaar bij de gast-familie Visscher in Dronten en het behalen van het atheneum diploma aan het Almere College in Kampen, besloot ze mee te loten voor de studie Ggeneeskunde. Ze werd ingeloot en met behulp van studentendecaan Paul Herfs en Jan Stoop werden verschillende stichtingen, fondsen en fundaties bereid gevonden om studiefinancering te verlenen, zodat zij geneeskunde kon studeren aan de Universiteit Utrecht. Tijdens haar eerste co-schap en Algemene semi-arts stage op de afdeling hematologie van het St. Antonius ziekenhuis, raakte ze gefascineerd door de hematologie. Maar ook de neurologie, waar ze kennis mee had gemaakt tijdens haar onderzoeksstage in het Zweedse Lund had haar interesse. Toen Douwe Biesma voorstelde onderzoek te doen naar de cardiovasculaire en neurologische complicaties bij Hodgkin patiënten nam ze het besluit om hematoloog te worden met aandacht voor de neurologie. In september 2006 startte zij met de opleiding tot internist in het St. Antonius ziekenhuis in Nieuwegein (opleiders: Douwe Biesma en later Tom Geers) en vervolgde deze vanaf 2011 in het UMC Utrecht (opleiders Elsken van der Wall, Douwe Biesma en Margriet Schneider). In 2012 startte zij met het enkelvoudig profiel hematologie (opleider: Reinier Raymakers). Elena onderbrak haar opleiding tot internist totaal anderhalf jaar om aan dit promotieonderzoek te werken. Elena is getrouwd met Bernie van Leeuwen; sinds 18 januari 2011 zijn zij de trotse ouders van Tim en in augustus 2013 verwachten zij hun tweede zoon.

11 List of abbreviations

ABVD:	adriamycin, bleomycin, vinblastine, and dacarbazine
AP:	angina pectoris
AR:	aortic regurgitation
AS:	aortic stenosis
BCVPP:	BCNU (carmustine), cyclophosphamide, vinblastine, procarbazine, prednisone
BEACOPP:	bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone
BEAM:	BCNU (carmustine), etoposide, Ara-C, and melphalan
BP:	blood pressure
CABG:	coronary artery bypass graft
CAC:	coronary artery calcium
CAD:	coronary artery disease
CAG:	coronary angiography
CCA:	common carotid artery
CI:	confidence interval
CVD:	cardiovascular disease
DC:	distensibility coefficient
DHAP:	dexamethasone, high-dose ara-C, cisplatin
EBVP:	epirubicin, bleomycin, vinblastine, prednisone
ECG:	electrocardiography
FU:	follw-up
IFRT:	involved field radiotherapy
IMT:	Intima media thickness
HL:	Hodgkin lymphoma
HLS:	Hodgkin lymphoma survivors
MI:	myocardial infarction
MOPP:	meclorethamine, vincristine, procarbazine, prednisone
MR:	mitral regurgitation
MS:	mitral stenosis
MRT:	mediastinal radiotherapy
NO:	nitric oxide
OPPA:	vincristine, procarbazine, prednisone, adriamycin
PET:	positron emission tomography
PR:	pulmonary regurgitation
PWVcf:	carotid-femoral Pulse Wave Velocity
RF:	risk factor

STNI:	subtotal nodal irradiation
TIA:	transient ischemic attack
TR:	tricuspid regurgitation
VIM:	etoposide, ifosfamide, methotrexate