Long-term side effects after treatment of Hodgkin's lymphoma

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All things are poison and nothing is without poison,
only the dose permits something not to be poisonous.

Paracelsus (1493–1541)

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Abstract

Background

Long-term side effects associated with the treatment of Hodgkin's lymphoma (HL) have frequently been reported during the last decades. Studies have shown increased mortality in HL survivors. Following Hodgkin's lymphoma, second malignancies (SM) and cardiovascular disease (CVD) are the most common causes of death in individuals treated for HL. This study investigates the incidence of side effects such as SM, CVD and infections in a cohort diagnosed with HL in Sweden between 1965 and 1995. In addition, this study identifies covariate risk factors for late side effects in order to develop strategies that prevent morbidity and mortality in HL survivors.

Methods

Using the Swedish Cancer Registry (SCR) at the National Board of Health and Welfare and the Multi-Generation Registry at Statistics (MGR) Sweden, we identified 6946 individuals diagnosed with HL between the years 1965 and 1995, and their first degree relatives (FDR) (n=17 858). In addition we identified the malignancies and inpatient care for CVD and infections for the HL cohort and their FDR. The standard incidence ratio (SIR) was calculated for the risk of SM, CVD and infections. For SM and CVD the risk also was stratified and calculated for family history of disease. The Swedish Hodgkin Intervention and Prevention study (SHIP), a prospective study, invited 702 individuals treated for HL at the age of 45 years or younger and who were treated in the regions of Skåne, Uppsala or Umeå. The participants completed a questionnaire and were invited to an out-patient visit to an oncologist with clinical examination and blood tests. Any pathological findings were referred for further investigation.

Results

An increased risk for SM in HL long-term survivors was observed and seems to increase with the number of FDRs with cancer. There was also an increased risk for inpatient care due to congestive heart failure (CHF) and coronary artery disease (CAD). A family history of CHF

and CAD further increased the risk for these diseases. The risk for inpatient care due to infections was increased and remained increased after 20 years or longer. The risk for infections was associated with splenectomy and hypothyroidism. Radiotherapy was an independent risk factor for cardiovascular disease in the cohort of the prospective study.

Conclusion

Long-term survivors from HL have an increased risk for developing late side effects such as SM, CVD and infections. Since many HL patients are young and the cure rate from the disease is high, it is of great importance to offer focused surveillance programs to selected individuals who are at high risk, e.g. individuals who received radiotherapy as part of their treatment and who have other known risk factors for cardiovascular disease such as hypertension, hypercholesterolemia, family history and smoking.

Abbreviations

HL	Hodgkin's lymphoma
SM	Second malignancy
CVD	Cardiovascular disease
SCR	Swedish cancer registry, National Board of Health
MGR	Multi-generation registry, Statistics, Sweden
FDR	First degree relative
SIR	Standard incidence ratio
SHIP	Swedish Hodgkin Intervention and Prevention
CHF	Congestive heart failure
CAD	Coronary artery disease
SALUB	Swedish working group for late effects after childhood cancer treatment
BCE	Before the common (Christian) era
DNA	Deoxyribonucleic acid
CT	Chemotherapy
RT	Radiotherapy
DBS	Double strand break
RS-cell	Reed-Sternberg cell
NLPHL	Nodular lymphocyte predominant Hodgkin's lymphoma
L&H-cell	Lymphocytic and histiolytic cell
LP-cell	Lymphocytic predominant cell
EBV	Epstein-Barr virus
HIV	Human immunodeficiency virus
cHL	Classical Hodgkin's lymphoma
DLBCL	Diffuse large B-cell lymphoma
IPS	International prognostic score
LAG	Lymphangiograpy
CTS	Computed tomography scanning
PET-CT	Positron emission tomography-computed tomography
LRCHL	Lymphocyte rich classical Hodgkin's lymphoma
EFRT	Extended field radiation therapy
MOPP	Mecloretamine, vincristine, procarbazine and prednisone
ABVD	Adriamycin, bleomycin, vinblastin and dacarbazine
GHSG	German Hodgkin's Lymphoma Study Group
COPP	Cyclophosphamide, vincristine, procarbazine and prednisone
BEACOPP	Bleomycine, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone
IF	Involved field
CHOP	Cyclophosphamide, doxorubicin, oncovin and prednisone
Gy	Gray, SI-unit for absorbed radiation dose (1 Gy = 1 J/Kg)

NHL	Non-Hodgkin lymphoma
ASCO	American Society of Clinical Oncology
LENT SOMA	Late Effects on Normal Tissue & Subjective and Objective observation, Management and Analytic procedures
OPSI	Overwhelming post splenectomy infection
EORTC	European Organisation for Research and Treatment of Cancer
ART	Assisted reproduction techniques
NPR	National Patient Registry, Swedish Social Board
HDR	Hospital Discharge Registry, Swedish Social Board
ICD	International classification of disease
PYRS	Person years
ITS	IT services and system development at Umeå University
UMDAC	Computer Centre of the University of Umeå
SPSS	Statistical Package for the Social Sciences
CI	Confidence interval
OR	Odds ratio
HL-BC	Breast cancer following Hodgkin's lymphoma
BC	Breast cancer
JNCI	Journal of the National Cancer Institute
VIP	Västerbotten Intervention Program
CAC-score	Coronary artery calcium score

Svensk populärvetenskaplig sammanfattning

Bakgrund

Hodgkins lymfom (HL) är en elakartad sjukdom som drabbar ca 170 individer i Sverige varje år, något fler män än kvinnor. Sjukdomen karakteriseras av förstorade, icke ömmande lymfkörtlar samt t.ex. nattsvettningar, viktnedgång, feber och klåda. HL är en av de tumörformer som studerats med avseende på sena biverkningar, bland annat på grund av att sjukdomen drabbar både barn och vuxna samt att överlevnaden efter behandling är hög.

Behandling av HL har varierat över tid. I början av 1900-talet gjordes försök med strålbehandling men resultaten var nedslående och gav på sin höjd tillfällig lindring av sjukdomssymtom. Bot var det inte tal om. När de linjära strål-acceleratorerna introducerades i mitten av 50-talet började en ny era för strålbehandling av cancer. Utvidgade externa strålfält, bland annat det så kallade mantelfältet, blev standardbehandling för Hodgkinpatienter med begränsad sjukdom (stadium IA och IIA). Målet var att, med "god marginal", behandla eventuell mikroskopisk sjukdom i lymfkörtlar ovan/nedanför diafragman för att ge ökad möjlighet till bot. Mantelfältet gavs mot halsen upp mot käkbenet, nacke, armhålor och brösthålan, inkluderande en stor del av hjärtat. Strålfältet omfattade även delar av brösten, framförallt hos kvinnor.

Sena biverkningar efter behandling av maligna sjukdomar har studerats sedan mitten av 1900-talet. Sedan slutet av 80-talet har forskningen accelererat i takt med ökad medvetenhet om omfattningen och de konsekvenser biverkningarna kan få för den enskilda individen. Sekundära tumörer och hjärtkärlsjukdomar är de två sena biverkningar som studerats allra mest. Muskelbesvär, nedsatt sköldkörtelfunktion och infektioner är exempel på andra, inte helt ovanliga biverkningar efter cancerbehandling.

Målet med studien var att, tillbakablickande, studera biverkningar i form av sekundär tumör, hjärtkärl sjukdom och infektioner, i en

grupp individer som fått behandling i Sverige, med bland annat utvidgade strålfält. Ett annat mål var att, framåtblickande, studera en grupp HL långtidsöverlevare och se hur de mår idag. Kan vi med strukturerad intervention förebygga insjuknande och dödlighet i symtomgivande sena biverkningar?

Material och metoder

Via Cancer Registret på Socialstyrelsen och Flergenerationsregistret på Statistiska Centralbyrån, identifierades
individer som erhållit HL diagnos i Sverige mellan åren 1965 och 1995 (n=6 946) samt deras förstagradssläktingar (FDR) (n=17 858). Förstagradssläktingar inkluderar föräldrar, syskon och barn. Såväl gruppen med HL patienter och gruppen med FDR matchades mot cancerregistret och slutenvårdsregistret för att identifiera förekomst av cancer och slutenvårdstillfällen pga hjärtkärl sjukdom och infektioner. Standard incidence ratio (SIR) för sekundär tumör, hjärtkärlsjukdom och infektioner beräknades. För sekundära tumörer och hjärtkärl sjukdom beräknades även risken relaterat till förekomst av cancer och hjärtkärlsjukdom i släkten.

Till den prospektiva, framåtblickande studien SHIP (Svensk Hodgkin Intervention och Preventions studie) inbjöds 702 f.d. HL patienter som behandlats i region Umeå, Uppsala eller Skåne, vid 45 års ålder eller yngre. De individer som accepterat deltagande i studien fick fylla i en enkät och erbjöds därefter ett läkarbesök med klinisk undersökning och samtal med läkare på onkologmottagning. Inför besöket togs blodprover. Om något avvikande noterades i blodprover, vid samtal eller undersökning remitterades individen för fortsatt utredning. Statistisk analys med logistisk regression utfördes på data från enkäten rörande hjärtkärl sjukdom och infektioner. Det gjordes även en bortfallsanalys på inbjudna individer.

Resultat

I den retrospektiva, tillbakablickande registerstudien noterades en ökad risk för sekundära tumörer bland HL överlevare, där det fanns en trend på en ökande risk med antalet förstagradsläktingar med cancer (SIR 2.26; 95% CI, 2.08-2.45, SIR 3.01; 95% CI, 2.57-3.51 och

SIR 3.45; 95% CI, 2.58-4.51, beräknat på 0, 1 respektive $\geq$ 2 FDR). Det fanns en ökad risk för inläggning på sjukhus pga hjärtkärlsjukdom, framförallt bland individer behandlade vid 40 års ålder eller yngre (SIR 2.63; 95 % CI, 2.13–3.20; 10-19 år efter HL). Bland dessa individer sågs efter 10-19 år en ökad risk för kranskärlsjukdom och hjärtsvikt (SIR 3.06; 95 % CI, 2.41–3.83 respektive SIR 3.45; 95 % CI, 1.65–6.34). För hjärtsvikt och kranskärlsjukdom sågs ytterligare ökad risk om det även fanns en familjehistoria med dessa sjukdomar. Risken för inläggning på sjukhus pga infektioner var ökad och riskökningen kvarstod även 20 år efter HL diagnos (SIR 2.94; 95%, CI 1.84–4.45). Av de 702 inbjudna långtids överlevarna var det 453 som skickade in en ifylld enkät. Ingen avgörande faktor för vem som deltog i studien kunde hittas. Från enkätdata i den prospektiva studien noterades att risken för svår infektion var fördubblad jämfört med normalbefolkningen. Risken var associerad med avsaknad av mjälte (OR 1.98; 95% CI, 1.23-3.18) och underfunktion av sköldkörtel (OR 2.33; 95% CI, 1.46-3.72). Strålbehandling och förhöjda blodfetter var oberoende riskfaktorer för att utveckla hjärtkärlsjukdom (OR 2.85; 95% CI, 1.19-6.80 and OR 4.93; 95% CI, 2.78-8.75).

Diskussion

Detta arbete har studerat långtidsöverlevare efter Hodgkins lymfom. Dessa lever med en risk för sena biverkningar efter sin behandling, bland annat i form av sekundära tumörer, hjärtkärl sjukdom och infektioner. Många patienter insjuknar i HL i unga år och deras chans till bot är stor. Det är därför viktigt att erbjuda strukturerade kontrollprogram efter behandling, till individer med hög risk att drabbas av sena biverkningar, t.ex. de som i unga år erhållit radioterapi som del i behandlingen mot HL och samtidigt har andra riskfaktorer för t.ex. hjärtkärlsjukdom. För den grupp individer vi studerat är behandlingen redan given med den tidens standardbehandling som gav god möjlighet till bot. Det vi idag kan påverka hos dem är övriga riskfaktorer (t.ex. rökning, höga blodfetter och högt blodtryck) och därigenom minska risken för sjukdom, s.k. primär prevention. Behandling av cancer tar idag hänsyn till den kunskap vi har om sena biverkningar, utan att äventyra chansen till bot. Idag följs barn och ungdomar som behandlas för cancer upp på

ett helt annat sätt jämfört med de yngre individerna i vår HL kohort. Svenska Arbetsgruppen för Långtidsuppföljning efter Barncancer (SALUB) arbetar sedan 2001 med att sammanställa uppföljnings-rekommendationer för olika cancerformer hos barn.

Original papers

The thesis is based on the following papers; they are referred to by their roman numerals.

I. Family history of cancer as a risk factor for second malignancies after Hodgkin's lymphoma; A Andersson, G Enblad, B Tavelin, M Björkholm, J Linderoth, I Lagerlöf, M Merup, M Sender and B Malmer. Br J Cancer (2008) 98, 1001-1005

II. Long-term risk of cardiovascular disease in Hodgkin lymphoma survivors – Retrospective cohort analyses and a concept for prospective intervention; Anne Andersson, Ulf Näslund, Björn Tavelin, Gunilla Enblad, Anita Gustavsson and Beatrice Malmer. Int J Cancer (2009) 124, 1014-1917.

III. Long term risk of infections in Hodgkin lymphoma long-term survivors; Anne Andersson, Gunilla Enblad, Anita Gustavsson, Martin Erlanson, Hans Hagberg, Daniel Molin, Björn Tavelin and Beatrice Melin. E-publication ahead printed version: Br J Haematol. 2011 Apr 7. doi: 10.1111/j.1365-2141.2011.08638.x.

IV. Cardiovascular side effects after treatment of Hodgkin's lymphoma – comorbidity factors and a strategy for intervention; Anne Andersson, Gunilla Enblad, Anita Gustavsson, Martin Erlanson, Hans Hagberg, Daniel Molin, Björn Tavelin, Ulf Näslund and Beatrice Melin. Manuscript.

Reprints were made with permission from Wiley-Blackwell (I and III) and British Journal of Cancer (II).

Introduction

Since the beginning of the 19th century, treatment of cancer has improved gradually. The flip side of the coin is the development of treatment-related long-term side effects that can cause severe morbidity.

Cancer – epidemiology and aetiology

Hippocrates (460-390 BCE) coined the word for cancer because the ulcerate tumours in breast cancer reminded him of a crab, *carcinos* in the Greek [1]. The oldest known human case of cancer is from ancient Egypt, 3 200-2 900 BCE. [2-3].

A malignant tumour cell is characterized by uncontrolled growth with the ability to invade and metastasize to other organs. That is, cancer cells do not respond to normal cell growth controlling signals. To get this ability the cell must undergo alterations in the deoxyribonucleic acid (DNA) [4-5]. There are a numerous cancers, each characterized from the cell of origin.

Inherited mutations or syndromes cause between 5% and 10% of all cancers. For the remaining 90-95 percent, the aetiology is often unclear, but environmental factors - such as diet, chemical, and radiation (ultraviolet and ionising radiation) exposure and infections, seem to play a role [6].

In 2009, 54 611 new cases (53% male and 47% female) were reported to the Cancer Registry in Sweden. The incidence of cancer is still increasing due to increased age, screening and improved diagnostic methods, but there is a trend for decreasing mortality, especially for patients between 15 and 74 years old (figure 1). In Sweden the most common cancer in women is breast cancer (28.7%) and the most common cancer in men is prostate cancer (35.7%). Hodgkin's lymphoma counts for less than 0.4 % of all cancer in Sweden.

Cardio vascular disease (40.1%) is still the most common cause of death in Sweden (2009). The second most common cause of death in Sweden is cancer. In 2009, 22 455 individuals (24.9 % of all deaths) died due to cancer; lung cancer was the most common cause of cancer death among women and prostate cancer among men[7].

Sweden
All sites but non-melanoma skin cancer
ASR (World) age (0-85+)
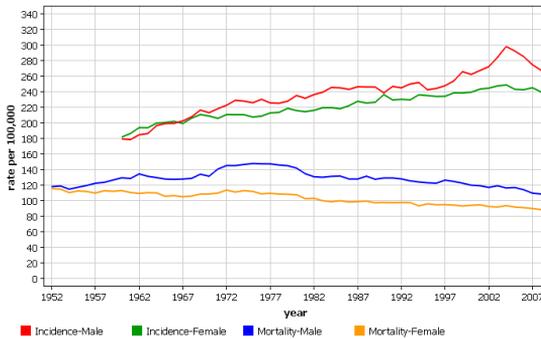
NORDCAN © Association of the Nordic Cancer Registries (7.2.2011)

Figure 1. Cancer incidence and mortality in Sweden 1952 (1960) – 2008, Engholm et al, Acta Oncol, 2010 [8].

Chemotherapy (CT)

The discovery of the cytotoxic effect of nitrogen mustard during the Second World War started an era of development of new cytotoxic drugs [9-10].

During the last decades, several cytotoxic agents have been developed and can be divided into groups according to their cytotoxic mechanism e.g. alkylating agents, antimetabolites, and antibiotics. Through the damage of different cell structures such as DNA and microtubuli, the cells undergo apoptosis. Malignant cells are in general more sensitive to chemotherapy than the normal cell since the chemotherapy acts on the proliferating cell and the cancer cell have a more rapid proliferation than the normal cell. With the aim of lowering the acute side effects of chemotherapy and increasing the anti-tumour effect, two or more cytotoxic drugs with different cyototoxic mechanism often are combined in the treatment of a malignancy. Clinical trials are crucial in the development of new treatment strategies of cancer [11].

Chemotherapy is used in the cure of cancer (alone or in combination with surgery and/or radiotherapy) and in the palliative setting. The impact of acute side effects from cancer treatment such as nausea, vomiting and neutropenic fever and sepsis, was a great problem, until the introduction of new modern antiemetic drugs and granulocyte

stimulating factor [12-13]. For some patient groups and individuals, however, acute side effects remain a medical problem, although to a much lesser extent.

Radiotherapy (RT)

In 1895 Wilhelm Conrad Röntgen (1845-1923) discovered X-rays trough the cathode-ray tube, a discovery that led to him receiving the first Nobel Prize in Physics 1901 [14]. In 1903 Marie Curie (1867-1934) shared the Nobel Prize in Physics with Pierre Curie and Henri Becquerel for their research with radioactivity. In 1911 Marie Curie also won the Nobel Prize in Chemistry for the discovery of radium and polonium, isotopes that later became useful as radiotherapy in cancer treatment [15].

Soon after these discoveries, in the late 1890ies, X-rays was used for treatment of e.g. superficial skin tumours. The use of radium for cancer treatment started in parallel with X-ray treatment. The first treatments consisted of a tube of radium held over the visible cancer for about 5-20 minutes twice a week for several months. Initially there was no knowledge about side effects or the dose limits for normal tissues, but experience eventually provided this knowledge [16-17] .

During the Second World War improvement in nuclear physics resulted in the development of artificial radionuclides. In the 1950s Cobalt^{60}, a synthetic radioisotope with much higher energy than radium, proved to be an effective treatment of cancer and provided the advantage of shorter treatment durations and an increased distance from patient to radioactive source [18].

In 1955, Henry Kaplan (1918-1984), introduced the first linear accelerator for medical use, a device that provided a major breakthrough in cancer treatment. Kaplan was also a pioneer in developing radiation field sizes, doses, and diagnostic staging techniques [19]. By the late 1950s the use of electrons with short penetrance started and gave the possibility to treat superficial tumours with minor side effects to deeper tissues.

Today, RT is an important part of curative and palliative treatment of malignant tumours. Although the target for RT is the tumour or the

tumour bed, it is inevitable that RT will affect normal tissue as well. To diminish damage to normal tissue so as to decrease the risk for acute and late side effects, type of radiation, the dose per fraction, number of fractions, target volume and intensity of the beam have been modulated over time [20].

Through a cascade of events including double strand breaks (DBS), ionising radiation causes DNA damage to the cancer cell and the normal cell, leading to cell death. As for chemotherapy described above, radiotherapy damage the proliferating cell as the cancer cell is more vulnerable for ionising irradiation since the cancer cell has a higher proliferation rate than the normal cell.

Hodgkin's lymphoma

In 1832 Thomas Hodgkin (1798-1866), a British physician, described a malignant disease involving lymph nodes and the spleen [21]. The disease was named Hodgkin's disease (later Hodgkin's lymphoma) and the symptoms included enlarged painless lymph nodules and splenomegaly.

In 1898 and 1902 Dorothy Reed and Carl Sternberg discovered a multinucleated cell – the Reed-Sternberg cell (RS-cell) - that is characteristic for Hodgkin's disease (Figure 2) [22-23]. Nodular lymphocyte predominant HL (NLPHL), is characterised by a variant of RS-cell, the lymphocytic and histolytic cell (L&H-cell, later called LP-cell or the "popcorn-cell") [24] (figure 2).
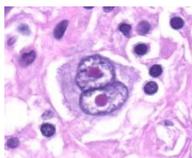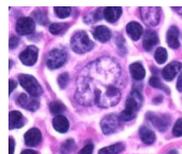
RS-cell   LP-cell (popcorn cell)

Figure 2. Microscopic pictures of the RS cell and the LP-cell. Printed with permission from Ramnani, D.M, Virginia Urology Pathology Laboratory, USA.

Infection, especially the Epstein-Barr virus (EBV) in mononucleosis, is one of the few highly suspected risk factors for development of HL[25-26]. This disease is common in childhood and adolescence which might explain the first incidence peak in younger individuals. Other possible risk factors are male gender, family history of HL and HIV infection [27].

HL neoplastic cells originate from B-cells. There have been several subclassification systems over the years. Today HL is divided into two groups; nodular lymphocyte predominant HL (NLPHL) and classical HL (cHL). This sub classification is based on the appearance of the cells at the microscopical level (Figure 3).

NLPHL accounts for <5% of the cases. The cells are CD20+, a characteristic that allows for the use of rituximab (targeted antibody therapy) in treatment. NLPHL transforms into DLBCL in about 5% of the cases. The outcome after treatment in this subgroup of DLBCL is similar as in de novo DLBCL [28].

Nodular sclerosis (NSCHL), the most common subtype of cHL, is characterized by lacunar cells and surrounded by collagen. Although classical RS-cells can be present in cHL, they are rare. In mixed cellularity cHL, classical RS-cell is present with a mixture of inflammatory cells in the background. Typically NSCHL results in supradiaphragmatic disease in a young individual without B-symptoms, and this is often associated with indolent behaviour. Subdiaphragmatic or extranodal disease is rare [29].Lymphocyte depleted cHL has a predominance of RS-cells in relation to background lymphocytes in contrast to lymphocyte-rich cHL where the opposite is shown. NLPHL is characterized by LP-cells surrounded by lymphocytes [29]. Lymphocyte-rich HL is characterized by RS-cells surrounded by lymphocytes, where eosinofils are rare or absent.
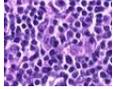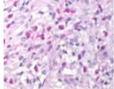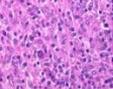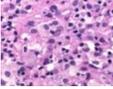
Group	Nodular Lymphocyte predominant	Classical HL			
Sub type		Nodular sclerosis	Mixed cellularity	Lymphocyte depleted	Lymphocyte rich
Microscopically appearance					
Frequency of cases	<5 %	70 %	20 %	<5 %	< 1%
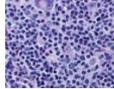
Figure 3. Microscopic appearance of the 5 subgroups of Hodgkin's lymphoma.
Pictures reprinted with permission from Ramnani, D.M, Virginia Urology Pathology Laboratory, USA respectively Karen Goddard, Vancover, www.pedsoncologyeducation.com.

In Sweden, 191 individuals (107 men and 84 women) were diagnosed with HL in 2009. There is a biphasic incidence peak at the age of 15-30 years and 50-70 years [7]. The incidence has decreased markedly between the years 1970 and 1990 whereas the opposite is found in non-Hodgkin lymphoma, indicating a shift in diagnosis [30].

The clinical appearance is typically painless enlarged lymph nodule(s) with or without weight loss, night sweat, fever, and/or pruritus. Pain in enlarged nodules following alcoholic consumption is classical, but uncommon [31]. In addition to lymph nodules the disease can engage the spleen and extranodal organs such as bone marrow and liver. Staging of the disease is decisive for treatment, according to the Ann Arbor staging classification modified by Cotswold (Table 1) and International Prognostic Score (IPS) (Table 2) [32-33].

Stage I	Single lymph node region or single extranodal organ or site
Stage II	Two or more regions on the same side of diaphragm, nodal and/or extra nodal sites
Stage III	Nodal involvement on both sides of the diaphragm and localized extralymphatic extension or splenic involvement
Stage IV	Dissemination to one or more extranodal tissues or organs, with or without nodal involvement
A	Asymptomatic
B	Night sweats, unexplained fever >38°C, unexplained weight loss (> 10%)
E	Extranodal disease
X	Bulky disease (>10 cm maximum diameter or mediastinal mass > one third of the maximal chest diameter
S	Engagement of the spleen

Table 1. Ann Arbor staging classification modified by Cotswold.

Gender	Male sex
Age	>45 years
Stage	IV
Albumin level	< 40 g/L
Hb	<105 g/L
Lymphocyte count	<8% or <0.6 x 10^9 cells/uL
Leucocytes count	>15 x 10^9 cells/L

Table 2. International Prognostic Score (IPS).

Between 1960 and 1980, when RT was standard treatment, staging laparotomy with splenectomy was the method of choice for defining the extent of abdominal disease. This procedure was combined with bipedal lymphangiography (LAG) and chest X-ray. In the 1990s, LAG was replaced by computed tomography scanning (CTS), to identify engaged lymph nodules [34].

In the late 1980s the use of splenectomy in staging HL decreased, as a consequence of increased use of combined chemotherapy and radiotherapy and the use of other prognostic factors for staging [35]. Today diagnostic work up consists of biopsy on enlarged lymph node, anamnesis, clinical examination, blood tests, positron emission tomography - computed tomography (PET-CT), diagnostic CTS and bone marrow biopsy (not in Stage IA and IIA) [36].

Treatment of Hodgkin's lymphoma over time

In parallel with other malignancies, HL is a fatal disease without treatment. Treatment tradition has varied over time and has also been affected by the stage of the disease. The curability rate for HL is high, and the primary aim with treatment is to achieve the best overall survival and progression-free survival, but toxicity (acute and late) and quality of life also has to be considered. During the last 40 years, several studies have resulted in reduced RT field and doses and increased use of supplementary chemotherapy. The increased use of combined therapy has improved survival rates [37-38].

At the beginning of the 20th century, the entire trunk was treated with weekly doses or a single dose. Since the results were poor RT was mainly given with palliative intention. In 1955 the first linear accelerator was used in medicine and Kaplan's research suggested that cure was possible for early stage HL [39]. The therapy was given with extended field radiation therapy (EFRT) so as to cover potential microscopic disease in adjacent lymph node areas.

Treatment areas were divided into supra and/or infra dia-phragmatic disease. Treatment of the upper half of the body included nodules localised sub mandibular, cervical, supra clavivular, infra clavicular, axillary, mediastinal, sub carinal and hilar. The method was named mantle field radiation due to its similarity with a mantle (clothing) that covers areas involved (figure 4).

Treatment of the lower part of the body included the splenic port and paraaortic, inguinal and femoral nodes. When no staging laparotomy and splenectomy were performed the whole spleen was irradiated. Radiation therapy with mantel field was used alone in early stages of disease (IA and IIA) and studies have shown ten year overall survival reaching 98% [40].
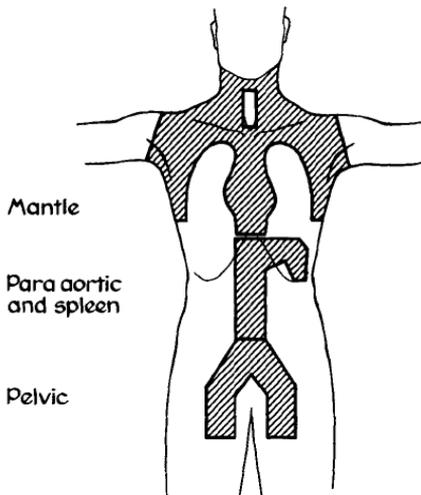
Figure 4. Schematic picture of the extended field used in HL treatment, including mantle field, splenic port and paraaortic, inguinal and femoral nodes. Reprinted by permission from Wiley (publisher). *Salzman JR and Kaplan HS. Effect of prior splenectomy on hematologic tolerance during total lymphoid radiotherapy of patients with Hodgkin's disease.* Cancer 1971;27:472.

In the 1960s, chemotherapy as single drug regiment was introduced for HL although the cure rate was poor. By the end of the 1960s, DeVita et al introduced the first combination therapy for HL, including mecloretamine, vincristine, procarbazine and prednisone (MOPP). The curability rate was 50-60 % in stage III and IV disease and the results were so dramatic that no further studies were needed to prove superiority [41]. For early stage disease, radiotherapy alone cured many patients. With the ambition of increasing the curability, programs with combination of full-dose chemotherapy and extended field radiotherapy was introduced.

In the 1970s chemotherapy with Adriamycin, Bleomycin, Vinblastin and Dacarbazine (ABVD) was introduced as an alternative for MOPP with equal survival [42]. At first ABVD was used when MOPP treatment failed and later ABVD was used in combination with MOPP. ABVD has now become the treatment of choice in patients 70 years or younger for all stages partly due to increased risk for acute myeloic

leukemia and myelodysplastic syndrome from the Mustine in MOPP [43-45].

Since 30-40% of patients with advanced HL progressed or relapsed on standard chemotherapy with MOPP/ABVD and had a poor response to salvage therapy, the German Hodgkin's Lymphoma Study Group (GHSG) conducted a study comparing COPP/ABVD (cyclophosphamide instead of mechlorethamine) and BEACOPP (bleomycine, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) in standard dose and dose escalated BEACOPP where the latter showed better disease control and overall survival than the two former [46-47]. The haematological side effects (leucopoenia, thrombocytopenia and anaemia) were higher in the increased BEACOPP arm, although manageable.

In the 1990s, prospective randomized trials were designed to reduce therapy for early stage HL to overcome late effects but still with preserved cure rates. As some oncologists thought RT caused long-term side effects, they relied on chemotherapy alone. The studies however showed a significant benefit in five-year freedom of disease progression when combining radiotherapy with chemotherapy [48].

Today, patients with stage I or IIA HL (<70 years) are primarily treated with chemotherapy (2-4 courses of ABVD) in combination with RT involved field (IF) (20-30 Gy). In advanced stages, stadium IIB – IV 6-8 courses of ABVD alternately 6-8 courses Bleomycine, Etoposide, Adriamycin, Cyclophosphamide, Vincristin, Procarbazine and Prednisone (BEACOPP) is standard treatment, if the patient is not included in a treatment study. Elderly patients (>70 years old) are treated with Cyclophosphamide, doxorubicin, Oncovin and Prednisone (CHOP) instead of ABVD, due to toxicity, otherwise, elderly are on the same schedule. For patients with NLPHL, rituximab could be considered [36]. A recent study from Germany shows that two cycles of ABVD in combination with 20 Gy involved field RT is as effective as four cycles of ABVD in combination with 30 Gy involved field RT [49].

Late effects

Survival from malignant diseases such as HL, testicular cancer and childhood cancer has improved. In malignant lymphomas, chemotherapy and radiotherapy are essential for the cure of the disease. Since the introduction of radiotherapy, the risk of side effects has been suspected. Several international studies have reported increased morbidity and mortality in long-term cancer survivors. Following death from HL, second malignancies and cardiovascular disease are the major cause of death in HL long term survivors [50-51]. There are other late side effects as well such as hypothyroidism, muscular atrophy, infections, infertility and fatigue, are also described. Possible side effects associated with long-term survival are not always strictly due to treatment - the impact of factors such as genetic predisposition, immunological factors and environmental factors should also be considered [52].

Radiotherapy has been ascribed the contribution of many of the side effects, and both fraction size and target dose seem to play a role. Target doses below 30 Gy seem to be safer than doses above 40 Gy, the typical dose used during the "mantle field era". The increasing awareness of late effects has influenced the way cancer is treated by encouraging the use of strategies that decrease morbidity and mortality [51].

Second malignancies (SM)

Second malignancy is any malignancy developed after treatment of a malignancy. Relapsed disease and metastasis with the same pathology as the first malignancy does not count as a SM. When calculating risk for second malignancy in studies, the first year often is omitted due to increased surveillance during work up. Described in the early 1960s second malignancy is one of the severe late effect associated with treatment of HL [53]. It is also the main cause of premature death among HL long-term survivors [50-51]. Several studies have shown that the incidence of SM increases after ten years latency and particularly among individuals treated at the age of 40 years or younger [54-56]. Radiotherapy has been suggested as the main cause of treatment-related solid tumours. Hodgson et al,

estimated a 30-year cumulative risk of second malignancy in HL diagnosed at 30 years or younger to be 18% in men and 26% in women, compared to a general population risk of 7% and 9% respectively [57].

Breast cancer, thyroid cancer, lung cancer, and gastrointestinal cancer are the most frequent second solid malignancies associated with the radiotherapy treatment of HL [54]. This could be explained by the fact that the whole thyroid gland and parts of the breast tissue and the lungs were included in irradiated area with mantle field, and that the gastrointestinal organs was partly included in abdominal irradiation fields. In combination with smoking radiotherapy gives an especially increased risk for lung cancer [58].

Chemotherapy is assumed to be the main underlying factor for haematological SM, which develops earlier than solid tumours as SM [59]. Treatment with MOPP has shown to increase the risk for acute myeloic leukaemia and myelodysplastic syndrome as late side effect, which was one of the main reasons to switch from MOPP to ABVD [43].
One can speculate if some of the HL were misdiagnosed Non Hodgkin Lymphoma (NHL) and that NHL as SM actually are disease relapse [30]. In addition, transformation from NLPHL to DLBCL could count for some NHL.

Cardiovascular disease (CVD)

CVD is the second most common cause of death in HL survivors [51, 60]. There is an increased risk for coronary artery disease, valve disease, congestive heart failure, pericardial disease, stroke, arrhythmia and sudden cardiac death [50, 61].
The main cause of radiotherapy-induced CVD is suggested to be inflammation in cardiac microvasculature as well as in arteries. The inflammation leads to micro-thrombi, vessel occlusion, decreased elasticity of the vessels and perfusion defects, all conditions that can cause ischemia. These damages in combination with hypercholesterolemia initiate the development of atherosclerosis [62]. Inflammation in the valve tissues produces fibrosis followed by decreased elasticity and impaired function [63]. Chemotherapy, on

the other hand, causes a direct myoepitelial damage and is correlated to cumulative dose [64].

As in SM, the risk for CVD in HL long-term survivors seems to be most pronounced in individuals treated at young age [65]. Mediastinal radiotherapy alone gives a four-fold increased risk for coronary artery disease. No additional increase of risk of coronary artery disease is shown when adding chemotherapy to treatment. The risk for congestive heart failure, on the other hand, seems to increase when RT is combined with antracyclin containing chemotherapy [61].

In a study of 415 HL patients with a median follow up of 11.2 years Hull et al. found that 5% of these HL patients had a significant clinical valve dysfunction 20 years after HL [66]. In 25 Swedish HL patients treated with only mantle field irradiation 11 (44%) showed abnormal valve structures 10-20 years after irradiation [67]. The systolic function and/or the diastolic function decreased in almost half of the patients. The study recommended reducing other risk factors for CVD in these individuals.

As the mantle field includes the carotid vessels, there is a risk of accelerating the atherosclerotic process [66]. Except increase risk for stroke due to valve disease, mantle irradiation can damage the carotid vessels and further potentiate the risk for stroke in HL survivors. Bowers et al, in a study of HL survivors and their siblings, found that the incidence for stroke among the siblings was similar for the general population. Compared with the cohort of their siblings, there was a four to five-fold increased risk for the HL survivors [68].

Asymptomatic and unknown cardiovascular disease can result in sudden death, which perhaps could have been prevented in an intervention program. There are no screening guidelines in place at the moment due to "the lack of direct, high-quality evidence on the benefits and harms of screening", according to the American Society of Clinical Oncology (ASCO) expert panel [69].

Other late effects

Hypothyroidism:
Treatment with mantle field irradiation included the whole thyroid gland that received substantial radiation dose. The radiation caused atrophy of the thyroid gland leading to an increased risk for developing hypothyroidism, a causal link and outcome that has been known since the early 1970s [70]. About 50% of patients with mantle field irradiation develop hypothyroidism [71]. The clinical presentations are symptoms that often affect quality of life, such as depression, fatigue, obstipation and bradycardia. Since metabolism is decreased, weight gain is common. The condition is treated with synthetic Levothyroxin, which in adequate doses has minimal side effects.

Muscular atrophy:
Patients treated with mantle field irradiation often present the classical atrophy of the muscles in the neck (Figure 5). There is frequently a marked border on the body that indicates where the RT was focused. The clinical symptoms are various - from no symptoms at all to substantial affect on the function of neck and upper extremities. The pain level differs between individuals [72]. The underlying cause of muscular atrophy has been regarded as a direct effect on the muscles through inflammation and fibrosis. Secondary effects as a result of damage to peripheral nerves has also been discussed [73]. The LENT SOMA scale (Late Effects on Normal Tissue & Subjective and Objective observation, Management and Analytic procedures) could preferable be used in the clinic so as to stage muscle atrophy [74].

In 2011 Van Leeuwen-Segarceanau et al. presented a study conducted on 12 patients treated with mantle field radiotherapy due to HL [75]. These patients were investigated using dynamometry, ultrasound and needle electromyography of muscles and ultrasonography. In 67% of the patients, the sternocleidomastoid muscle was severely atrophic. The Dutch group suggested damage in micro vascularisation causing myogenic damage. Muscle atrophy outside the radiation field is likely due to neuropathic damage. In more severe cases surgery with posterior spinal arthrodesis could be considered [76].

Figure 5. A 54 year-old man who was treated for HL (stage IA) with mantle field irradiation, 40 Gy at the age of 29 - 25 years before the picture was taken. The right picture illustrates full extension in the neck. This disablement is affecting quality of life considerably. The patient consented to the publication of the pictures.

Fatigue:

Long-term survivors of cancer experience increased fatigue compared to the general population. In HL survivors, fatigue seems to be more prevalent than for other cancer survivors. Fatigue is characterized by extreme tiredness, decreased energy and reduced muscle strength. Presence of B-symptoms at diagnosis (unexplained fever, weight loss and night sweats), social isolation and presence of pulmonary toxicity (e.g. pneumonitis and dyspnoea) has been suggested as predisposing factors [77]. A Norwegian study of 476 HL survivors reported that many individuals with chronic fatigue recover and that persistent chronic fatigue was found especially in individuals with B-symptoms at diagnosis [78].

Infections:

In the cell mediated immune defence, the spleen is important, especially against encapsulated bacterial organisms, e.g. streptococcus pneumonia. Until the early 1990s, splenectomy was a standard procedure for HL work up. Studies have shown an increased risk for infections in HL survivors where overwhelming post splenectomy infection (OPSI) is the most feared condition as it has a high rate of mortality [79]. To avoid OPSI, splenectomized patients should be offered pneumococcal vaccination at regular intervals [80]. British guidelines from 2009 suggest pneumococcal vaccination as well as vaccination for haemophilus, meningococcus and influenza for asplenic patients [81].

Infertility:

Treatment of cancer with chemotherapy at young age can result in infertility, depending on the gonadotoxic effect of the drug. Treatment causes DNA damage in ovarian follicles and in testosterone producing Leydig cells in the testes. Chemotherapy also damages the germinal epithelial cells in the testes [82]. Male post-treatment infertility is studied more frequently than female infertility. In an EORTC study from 2007, recovery of gonadal function in men after treatment with alkylating agents (e.g. MOPP) was seen in 26% of patients after three years. In men treated with non-alkylating agents (e.g. ABVD), recovery rate after three years was 83% [83].

Parenthood in 602 HL relapse-free long-term survivors, treated between 1971 and 1998, was investigated in a Norwegian study. They found that 68% succeeded to become parents without assisted reproduction techniques (ART). All the individuals desiring to become parents in the study were <40 years and childless at HL diagnosis [84]. Examples of ART are cryopreservation of semen or fertilized oocytes, intrauterine insemination, in vitro fertilization and intra cytoplasmatic sperm injection. Today fertile men in Sweden are offered cryopreservation of semen before treatment of a malignancy. Cryopreservation of ovarian tissue, embryos or non-fertilized eggs is sometimes offered fertile women.

Prevention

A risk factor for a disease is a factor that plays an essential role in the development of a disease. Smoking, hypercholesterolemia and hypertension are examples of well-known risk factors for CVD [85]. By eliminating a risk factor, the risk for the disease is reduced. A risk indicator for a disease, on the other hand, coexists with an increased probability for development of a disease. An example of a risk indicator for cardiovascular disease is girth >88 cm in women.

Primary prevention can decrease the risk for a disease in individuals not affected. For example, cessation of smoking decreases the risk for the development of lung cancer. Secondary prevention can prevent recurrence in an individual who has suffered from a disease. Treatment of hypertension, for example, can help prevent a recurrence in cardiovascular disease.

Registries in Sweden

Using different types of registries can produce important research. The number and quality of registries in the Swedish health care system increases every year - a trend that can promote research opportunities.

To facilitate epidemiological and clinical research on malignant disease and to map its incidence over time, all malignant tumours since 1958, are by law reported to the Swedish Cancer Registry (SCR), at the National Board of Health and Welfare. Since the 1980s, six local oncological centres are responsible for the registrations [7].

Registration of diagnoses from inpatient care to the National Patient Registry (NPR), also referred to as the Hospital Discharge Registry (HDR), was started at the National Board of Health Care in 1964, but at first it was limited to experimental work in the region of Uppsala. In 1987 hospital discharges from the whole country were registered [7].

In 2000, the first version of the Multi-generation registry (MGR) at the statistics, Sweden, was created. In 1947, all residents in Sweden at the age of 15 years or younger and their parents were counted and received a unique identification number based on date of birth.
Therefore MGR is based on all individuals recorded in Sweden since 1961 and born 1932 or later. Since the registry is based on individuals born 1932 or later and recorded in 1947 or later, information for the complete nuclear family for all individuals is not available. The registry is updated every year [86].

Materials and methods

The cohort studied consists of individuals diagnosed with HL in Sweden between 1965 and 1995, a period when radiotherapy with extended fields was common. From the Swedish Cancer Registry 6 946 individuals were identified. When collecting diagnoses (second malignancy, cardiovascular disease and infection) for the retrospective studies of late effects, the first year after HL diagnosis was omitted to avoid including diseases noticed during HL work up, noticed as the result of increased surveillance during treatment or being acute side effects of treatment of HL.

Material and methods – Retrospective study

The retrospective study was based on the 6 946 individuals diagnosed with HL between 1965 and 1995.

First degree relatives (FDR), including parents, children and siblings, of the HL patients, were identified through the Multi-Generation Registry in Sweden. Of the 17 858 identified FDR, 4 440 were parents, 4 611 siblings and 8 807 were children.

In paper I, we matched all HL patients and their FDR to the Cancer Registry from where any cancer diagnoses and diagnose year were registered for each individual. In paper II and III, we matched the cohorts of patients and FDRs to the Swedish Hospital Discharge Register (HDR) to find inpatient care for CVD and infections with CVD or infection as the first diagnosis code. CVD or infection as first diagnosis code was set to be a severe incidence of the disease registered. ICD-10 was used to identify the diagnoses of interest, and was then converted to diagnosis codes in ICD-9, ICD-8 and ICD-7, using converting tables from the Swedish National Board of Health (table 3).

	ICD 10
Coronary artery disease	I20-25.0-9
Valve disease	I08.0-9, I34-37.0-9
Cardiac arrest	I46.0-9
Arrhythmia	I48-49.0-9
Heart failure	I50.0-9
Stroke	I63-67.0-9
Diabetes	E10-11.0-9, E13-14.0-9
Infections	A39-41.0-9, A49.0-9
Cardiac disease UNS	I51.0-9

Table 3. Diagnosis used in the retrospective analysis from the Swedish Hospital Discharge Registry. Diagnosis shown is ICD10 (Swedish version used from 1997 and ongoing). Diagnose codes were converted from ICD 10 – ICD 7 trough converting tables at the Swedish National Board of Health (ICD 7: 1958-1968, ICD 8: 1969-1986, ICD 9: 1987-1996).

The Swedish National Board of Health creates incidence files on cancer for the general population in Sweden, which is updated every year. Because no such incidence files were available for CVD and infections, they had to be constructed using the 9.5 million observed inpatient registrations from the whole HDR. The inpatient registrations were categorized for calendar year, sex and five-year age group. Expected number of cases was calculated by multiplying the person years for every calendar year, sex and five-year age group by the corresponding age-specific incidence rate created from the HDR.

Standard Incidence Ratio (SIR) for cancer, CVD and infections in the HL cohort compared with general population were calculated using person years (PYRS). This calculation was done by dividing the number of observed cases in the cohort by the number of expected cases (paper I, II and III).

The impact of family history of cancer and CVD was investigated in papers I and II. SIR was calculated, as above but selected for positive or negative family history of the disease of interest. For cancers the selection was on 0, 1 or $\geq$ 2 FDR with cancer. Cause of death among the 4 912 deceased individuals in the HL cohort was registered through the cause of death registry.

Material and methods – Prospective study

For this prospective study participants were selected from the HL cohort (n=6 946 individuals) who were still alive 1 January 2005, were treated at the age of 45 years or younger and were diagnosed in the regions of Umeå, Skåne or Uppsala. Consent to contact the patients was obtained from their attending physicians.

   A written information and inquiry to participate in the study was sent to the patients. The individuals who accepted the invitation received a questionnaire that asked questions about their HL disease and treatment, health status, socio-economic status, and family history of cancer and CVD. After completing the questionnaire the HL patients were offered an open clinic visit with an oncologist for clinical investigation, laboratory tests and discussion. Any pathological findings uncovered during the clinical examination, anamnesis or in the lab test resulted in referral to a dedicated specialist or to a supplementary investigation.

Data from the questionnaires were scanned using help from by IT services and system development at Umeå University (ITS - former UMDAC, Computer Centre of the University of Umeå) and were analysed with the Statistical Package for the Social Sciences (SPSS 17.0) software. Data for infections and cardiovascular disease in the HL cohort were analyzed for covariates with univariate and multivariate logistic regression analysis. In paper II, a pilot study of 47 individuals from the region of Umeå, was presented to test the feasibility of the Swedish Hodgkin Intervention and Prevention (SHIP) study.

Statistical methods

Standard incidence ratio (SIR) was calculated using the statistical method person year (PYRS). PYRS is suitable when comparing observations and expected cases in e.g. malignant diseases. For every individual in the cohort PYRS is calculated starting one year after HL diagnosis and ends at time of death or at the end of follow up (2004-12-31). Using PYRS allows for a calculation based on person years of observation after exposure (HL diagnoses) in each individual. Data is adjusted for age, sex and survival. However, 20 years of follow up in

this setting could represent one individual with 20 years of follow up or ten individuals with two years each of follow up. To avoid this weakness of the method, Shoenberg and Myers suggested that the cases should be compared in specified post treatment time periods [87].

To calculate the risk of a specific condition in the HL cohort compared to the Swedish population we needed the incidence file for the condition in the whole Swedish population. An incidence file was created using 9.5 million observed inpatient registrations from 1964 through 2005 (data collected from the whole Hospital Discharge Registry). From this information, we categorized variables for calendar year, sex and age. Using this incidence file we calculated the expected number of cases of a condition by multiplying the person years for each calendar year, sex and five-year age group by the corresponding age-specific incidence rate created.

Regression analysis was used in the prospective cohort analysis. Using this statistical model we could analyse whether an outcome for a dependent variable (e.g. cardiovascular disease) is affected by other independent variables (e.g. radiotherapy and splenectomy). We mainly used binary logistic regression analysis in a univariate (one dependent and one independent) or multivariate (one dependent and one or more independent) setting and calculated odds ratios (OR). Calculations in the multivariate model were adjusted for gender and age.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 17.0) software.

Results

From the Swedish Cancer Registry 6 946 individuals diagnosed with HL in Sweden between 1965 and 1995 were identified and 17 858 first-degree relatives were identified using the Multi-Generation Registry at Statistics, Sweden. At the end of the follow up (31 December 2004) 2 034 individuals were alive. In HL individuals treated at the age of 40 year or younger the survival rate was decreased compared to the general population in Sweden (figure 6).
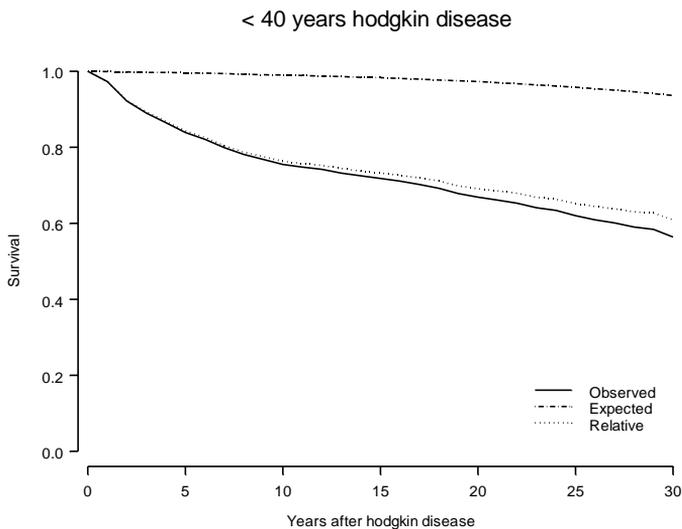
< 40 years hodgkin disease

Figure 6. Survival in individuals treated for HL in Sweden at the age of 40 or younger. Reprinted with permission. Andersson et al. Family history of cancer as a risk factor for second malignancies after Hodgkin's lymphoma. Br J Cancer (2008) 98, 1001 – 1005.

Retrospective cohort

In paper I, 781 second malignancies were found in the HL cohort; 645 (82.6%) were solid tumours and 136 (17.4%) were haematological malignancies. Compared to the general population in Sweden, the SIR for second malignancies in the HL overall cohort, 10-19 years after diagnosis, was 2.62 (95% CI, 2.32-2.96) and for individuals diagnosed before the age of 40 years SIR for second malignancy was 4.34 (95% CI, 3.51-5.30). One year or longer after HL diagnosis there was a trend in the whole cohort; the risk for second malignancies increased

as the number of first-degree relatives with cancer increased (SIR 2.26 to 3.01 and 3.45 (0, 1 respectively >2 first degree relatives with cancer)). A significant increased risk for breast cancer was seen 10-19 years after HL (SIR 2.22; 95%CI, 1.76-2.76). When subdivided by age at diagnosis, a significant increased risk was only seen in women treated for HL at 40 years or younger (SIR 5.20; 95% CI, 3.39-7.62). In the cohort of relatives there was no increased risk for cancer compared to the general population in Sweden.

Paper II uncovered 1 413 registered events of inpatient care for cardio vascular diseases in 698 (15%) individuals from the HL cohort. The risk for CVD, especially increased among individuals treated at the age of 40 years or younger (SIR 2.63; 95% CI, 2.13-3.20). After 10-19 years, an increased risk for coronary artery disease was shown in individuals treated at a young age (SIR 3.06; 95% CI, 2.41-3.83). With a family history of coronary artery disease SIR was even higher (SIR 5.53; 95% CI, 3.89-7.62). Twenty years or more after HL diagnosis, SIR for the development of congestive heart failure was 10.1 (95% CI, 8.03-12.64) and 25.0 (95% CI, 3.30-42.75) (0 and > 1 first degree relative with heart failure). Eighty-one individuals treated at a young age developed valve dysfunction 20 years or more after HL diagnosis (SIR 26.55; 95% CI, 1.08-33.00).

Paper III found that long-term survivors of HL had an elevated risk for infection 1-9 years after diagnosis (SIR 6.03; 95% CI, 4.53-7.86). The risk remained elevated even after 20 years or longer (SIR 2.94; 95% CI, 1.84-4.45).

Prospective cohort

Paper II presented the feasibility study where 35 of 47 invited individuals returned the completed questionnaire. No indignant reactions from the participating individuals were observed.

Paper III presented data from the questionnaire concerning infections after HL treatment; the univariate logistic regression analysis for hospitalization because of severe infections among HL long-term survivors had an OR of 2.13 (95% CI, 1.35-3.36) in the splenectomised group. In the group of individuals with hypothyroidism, OR was 2.59 (CI 95%, 1.64-4.08) for hospitalization for infections. The odds ratio for both these factors remained significant in a multivariate analysis (OR 1.98; CI 95%, 1.23-3.18 and

OR 2.33; 95% CI, 1.46-3.72 respectively). Paper III also presented that 74.5% (453/702) accepted to participate in the prospective study and completed the questionnaire.

In paper IV radiotherapy and hypercholesterolemia were shown to be independent risk factors for the development of CVD in a logistic regression analysis (OR 2.85 95% CI 1.19-6.80 and 4.93; 95% CI, 2.78-8.75 respectively). Radiotherapy and hypercholesterolemia increase the risk for the development of valve disease (OR 4.06; 95% CI, 1.18-13.91 and OR 2.69; 95% CI, 1.39-5.21 respectively).

Median age of CVD was 48.9 years and the median latency was 22.0 years. The incidence of valve disease seems to accelerate ten years after treatment of HL, whereas coronary artery disease and heart failure seems to increase earlier. After 30 years, 15 % of the long term survivors in the prospective cohort had developed coronary artery disease, valve disease or heart failure (figure 7).
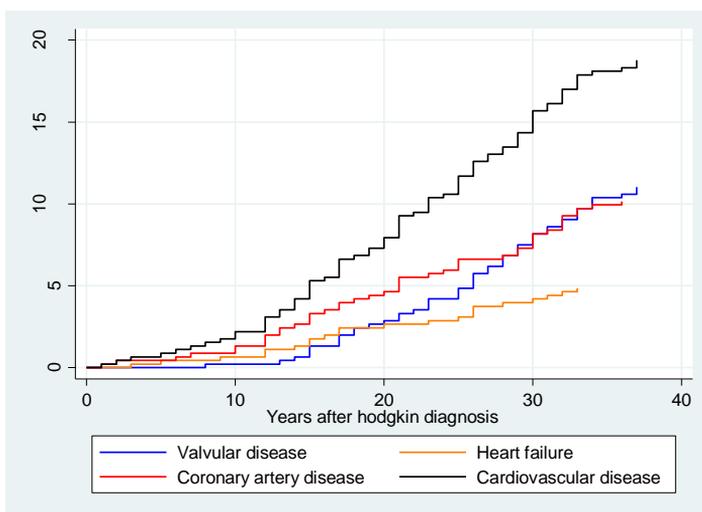

Figure 7. Latency from HL diagnosis to first incidence of cardiovascular disease in 453 HL long term survivors. Cardiovascular diseae includes valve disease, heart failure and coronary artery disease. Coronary artery disease includes myocardial infarction.

Discussion

There is a general opinion worldwide that HL survivors at high risk for severe late effects should be offered prevention and screening to decrease morbidity, and mortality associated with their treatment [88-89]. However, there is no general agreement on what, when or how often this should be done [90]. To this end, our studies examine the risk for late effects in a cohort of Swedish HL patients, identify co-morbidity factors and to initiate a prospective intervention study among HL long-term survivors. Through the prospective study a structured surveillance program was offered with the aim to prevent morbidity and mortality in HL survivors at high risk for severe late effects. The cohort studied is long-term survivors diagnosed with Hodgkin's lymphoma in Sweden between 1965 and 1995. Radiation therapy has been ascribed the main contribution to late effect and 1965 to 1995 was an era when mantle field irradiation was standard treatment in early stages of the disease.

Our study found an increased risk of premature mortality, second malignancy (SM), cardiovascular disease (CVD) and infections in HL long-term survivor, a finding that has been confirmed in several other studies [50-51, 56, 60-61, 91]. We also found that splenectomy and hypothyroidism are independent risk factors for the development of late infections among HL long term survivors. The novel finding that hypothyroidism is an independent risk factor for the development of infections in HL survivors is to our knowledge not described in other studies. Radiotherapy was shown to be an independent risk factor for CVD, and especially valve disease. Hypercholesterolemia was an independent risk factor for both coronary artery disease and valve disease. Some of the well-known risk factors for CVD among the general population (such as hypertension and smoking) were independent risk factors in the univariate model but not in the multivariate model, perhaps reflecting small sample size in the SHIP study. Our study shows that a positive family history of cancer seems to further increase the risk for SM among HL survivors, a finding presented in one earlier study [92]. In that study, a total of 7 476 individuals from Sweden and Denmark, with HL lymphoma were studied: the Swedish cohort was diagnosed between 1974 and 1990 and partly overlapping with our HL cohort. A family history of

coronary artery disease and heart failure increased the risk for these diseases.

It is common to omit the first year after diagnosis when studying late effects after treatment of HL [55, 93]. This one-year delay avoids inclusion of events that are detected by chance during clinical work up and treatment as these events should not be interpreted as late effects. Any CVD or infection during this first year should be calculated as acute side effects from treatment: however is one year the optimal period? In this study breast cancer that developed two years after treatment is considered a second malignancy but the cancer probably already existed, although non-detectable, at the time of HL diagnosis. The localisation of a second malignancy due to radiotherapy should also be found in the irradiated area or in its surroundings. This however, is hard to do in large registry studies where treatment data is limited. In the future, data from local or national registries could simplify these studies when e.g. when pathological and treatment data are available.

Breast cancer in HL survivors

Our study shows an increased risk for breast cancer in women treated for HL at the age of 40 years or younger, which has been shown earlier [91, 94]. Radiotherapy has been implicated as the major cause of solid tumours in second malignancies. Since the RT dose and field size have been reduced, the risk for breast cancer in HL survivors has decreased [95]. A family history of overall cancer increases the risk for breast cancer even further, a conclusion that i also espoused by Landgren, et al [92]. Family history of breast cancer, on the other hand, does not seem to influence the risk further, a finding also supported by other studies [96]. Chemotherapy- or radiotherapy-induced ovarian dysfunction during HL treatment has been shown to diminish the increased risk for breast cancer in HL survivors, presumably reflecting the hormone influence on promoting tumourigenesis in breast cancer [97].

In contrast to earlier studies an Italian study recently presented decreased OS (48% vs 69%, p<0.0001) among individuals with breast cancer following HL (HL-BC) compared to novel BC [98]. The

increased mortality, however, was mainly due to an increased risk for death in overall cancer and CVD. Women with HL-BC tend to be younger at breast cancer diagnosis and the tumours are poorer grade and more frequently estrogen and progesterone receptor negative [99]. The HL-BC patients also seem to receive less antracycline-containing chemotherapy and post-operative irradiation, as the result of earlier treatment of HL [97]. Since breast cancer is the most frequent cancer among women in general (a lifetime risk >10%) this four-fold increased risk for HL survivors is clinically relevant. Starting ten years after HL treatment, mammography screening should be offered women treated at 40 years or younger and with part of breast irradiated. No consideration should be taken for the presence or absence of ovarian dysfunction, since these factors should be assumed to be risk modulators.

Cardio vascular disease in HL survivors

Increased risk for CVD was shown in HL long-term survivors, a finding corroborated in earlier studies [61, 89]. Specifically, increased risk of coronary artery disease, valve disease, and congestive heart failure was presented. The risk for coronary artery disease was increased three-fold in individuals treated at the age of 40 years or younger 10-19 years after HL diagnosis. Young individuals with family history of coronary artery disease showed an even higher risk (SIR 5.53; 95% CI 3.89-7.62) 10-19 years after HL diagnosis. In the retrospective registry study an increased risk of valve disease was shown 20 years or longer after HL. In the SHIP-study, where self reported data was collected, the development of valve disease accelerates ten years after HL. A Norwegian study suggested echocardiography screening in HL survivors at risk since they found pathological valves in almost 25% of the 116 studied survivors [100].

Family history of CVD, hypercholesterolemia, hypertension, and smoking are well-known risk factors for the development of CVD in the general population [6, 85, 101-103]. Our study confirms that these risk factors also are important for the development of CVD in HL long-term survivors. In surveillance programs risk factors such as hypercholesterolemia and hypertension should be monitored and treated to help prevent CVD.

Symptoms associated with the heart, especially in younger individuals without previous CVD history, can easily be mistaken for musculoskeletal symptoms, gastric ulcer or anxiety. Without the knowledge about the risk for CVD in the cohort of HL survivors, general practitioners and HL survivors could miss cardiac symptoms, resulting in unnecessary suffering, increased costs for the society, and in the worst scenario, the development of fatal disease.

Infections in HL survivors

Few studies have examined infections as late side effects. Most studies have focused on splenectomy and its influence on infections [104-105]. The registry study and the study on the SHIP cohort retrospectively found an increased risk for infections in HL long-term survivors. The risk seems to remain after 20 years. In the SHIP cohort, splenectomy and hypothyroidism were independent risk factors for developing infection. One possible explanation for hypothyroidism being a risk factor for infections could be that a larger radiotherapy dose was received in individuals developing hypothyroidism and that this high biological dose also damaged cilia in the upper respiratory tract.

Splenectomies decrease an important part of the immune defence against encapsulated bacteria such as pneumococcus and meningococcus. To decrease the risk of overwhelming post splenectomy infection (OPSI) regular vaccination against pneumococcus is essential (Landgren*, et al* 2004). OPSI is a rare condition but when it appears it is life threatening [79]. In our registry study, no treatment data were available. Relapsed HL and SM were not omitted from the study. A possible weakness in our study is that infections related to acute side effects from chemotherapy directed at relapsed HL and SM were included.

The risk in the SHIP cohort is slightly lower, which perhaps reflects the risk for infection where no acute treatment-related infections are included. Of course, each study used a different sample size and the statistical methods differ and therefore the numbers are not fully comparable. Spelenctomised individuals in the SHIP study who were

not under any pneumococcal vaccination program were admitted to the infection or internal medicine department for regular vaccinations every fifth year, in line with current recommendations.

Cause of death among HL patients

As in other studies [50], we found that the mortality in HL survivors, treated at the age of 40 years or younger increased compared to the general population. HL relapse was the most frequent cause of death and second malignancy and cardiovascular disease were the second and third most frequent causes of death respectively. In the Swedish HL cohort, 852 (17.3%) of the deceased individuals were treated at the age of 40 years or younger, with a mean survival after HL of 4.97 (0-37) years, whereas the mean survival was 0.97 (0-36) years for individuals treated when they were older than 40 years old. In the younger cohort, 63.1% died due to HL, 24.8% died due to second malignancy and 8.3% died due to CVD. The corresponding figures in the older cohort were 47.1, 27.2 and 14.0% respectively (unpublished data).

Aleman et al studied the cause of death among diseased individuals treated for HL at the age of 40 years or younger, where 54.6% died due to HL, 21.7% by second malignancy, and 9.4% due to CVD.

These percentages correlate well with our data from the Swedish cohort. The treatment of the two cohorts differs presumably because the American cohort was treated between 1965 to 1987 and our cohort was treated between 1965 and 1995 [50].

In the general population, cardiovascular disease is the major cause of death today. The mean length of life in the general population in Sweden today is 83.1 years for women and 78.9 for men. Hancock et al presented significant increased risk for cardiac mortality only in individuals who received more than 30 Gy to the mediastinum, but these data have not yet been confirmed by any other study [106]. However several studies indicate decreased risk for CVD as late side effect since the treatment has been modified to lessen the irradiation doses to the heart [107].

Radiotherapy in HL treatment

With the knowledge of late effects after treatment of HL, particularly the radiotherapy, one can ask if it is really necessary to continue to irradiate HL or is it possible to cure the disease with chemotherapy only.

In JNCI, 2009, Longo questioned the retaining of treatment with radiotherapy for HL, since the obvious risk of both severe and less serious side effects has been shown repeatedly [108]. He claimed that chemotherapy has shown considerably less severe side effects and has the potential to cure HL without the addition of RT. Longo states the polemic this way: "Noncurative doses of chemotherapy are combined with noncurative courses of radiation therapy in most cases. Why?" He also points out that there is no evidence that lowering the RT doses will reduce the risk of toxicity: "it is simply unjustified to keep using a toxic modality for the next 10-20 years while safety data are collected and analysed".

Aleman et al. responded to the critique that it is not possible to achieve as good cure rates with chemotherapy alone, as we get with combined therapy according to present evidence. [109]. They also responded by stating that RT reduces local recurrence, since relapse often involve primary site of HL. Aleman refers to studies that conclude that there is a reduced risk for breast cancer and lung cancer in HL survivors treated at lower doses and reduced field size [90, 95]. It has also been indicated that there is dose-effect and dose-volume relationships for cardiovascular disease following mediastinal irradiation [107]. This is one of the reasons why radiotherapy still has its place in treatment of HL, even though avoiding radiotherapy as part of treatment could be considered in individuals at high risk for CVD.

Swedish Hodgkin Intervention and Prevention – SHIP

The knowledge about late side effects after treatment of malignant diseases has improved substantially over the last 30 years. Since 2001, The Swedish working group for late effects after childhood cancer treatment (SALUB) have worked to compile follow-up recommendations after cancer treatment in children, the patient

group with the highest cure rate but also with the greatest risk for developing late side effects of treatment [110]. That treatment should have been given to the HL cohort is unquestionable since the disease was potentially life threatening without treatment.

The initial start point of the study was a concern in the Swedish Hodgkin Lymphoma Group that HL survivors did not have sufficient information and adequate surveillance. Our aim was to study the condition of these survivors and the frequency of their long-term regular check-ups. In addition, we offered a structured surveillance program for individuals at high risk for late effects. The pilot study confirmed the feasibility of the study and the reactions from the participants were positive.

The Västerbotten Intervention Program (VIP) is an intervention program with a similar design as the SHIP-study [111]. VIP also uses a questionnaire that asks questions about life style issues and lab tests. This information is then used to provide a patient-specific recommendation according to a patent's risk profile. VIP was extended from a community based study in Västerbotten showing 19% reduction in risk for cardiovascular disease in the intervention group [112].

The knowledge of covariate risk factors can give the health care system an opportunity to prevent severe late side effects in individuals at high risk and perhaps even prevent premature mortality in HL survivors. Ng et al. presented a summary of second malignancies and cardiovascular disease that suggested strategies for prevention including patient education and for early detection of severe late effects in high-risk patients [90]. Such strategies were recently presented by a Dutch study suggesting screening for CVD every fifth year for CVD after five in individuals with high risk for CVD and after ten years in the other HL survivors. The screening methods included coronary artery calcium score (CAC-score), CT-angiography, echocardiography or electrocardiogram, depending on whether cardiac symptoms was present or absent [113]. They also suggest monitoring of general risk factors for CVD. There is also a need to evaluate if such strategies have any impact on survival of HL survivors and if they are cost effective.

These patient education strategies that illuminate the risks for long-term side effects and the advantage of a structured surveillance program for high-risk individuals are in line with the design of the SHIP study. Patient education could help patients influence their own health by encouraging them to stop/avoid smoking and to adopt a healthy life style

Conclusion and future perspectives

The success of cancer treatment has resulted in increasing the numbers of long-term cancer survivors around the world. Since individuals affected by Hodgkin's lymphoma often are young and the treatment is successful, the number of HL long-term survivors is substantial. Treatment with mantle field irradiation and antracycline-containing chemotherapy can result in serious and sometimes fatal side effects, yet HL patients and health care providers are not always aware of these side effects and how to deal with them. In addition, the mortality among HL long-term survivors is increased compared to the general population.

There is a common opinion that HL long-term survivors are at high risk for developing potentially life threatening late effects and because of this they should be offered intervention and prevention. The optimal methods and interval for this remain unclear: however the ongoing prospective SHIP study could provide some answers to these questions.

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