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Survival and treatment related toxicity in classical Hodgkin lymphoma

INGEMAR LAGERLÖF



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Abstract

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Treating early-stage classical Hodgkin lymphoma (cHL) by adding radiotherapy to chemotherapy gives better disease control compared to chemotherapy only. With a low median age at diagnosis, the risk from cHL needs to be weighed against the risk of treatment toxicity. Historical reports indicate substantial toxicity from radiotherapy, with excess morbidity and mortality. These results are based on radiotherapy techniques no longer in use. Modern radiotherapy might not cause the same level of long-term risks.

By linking lymphoma registers and health registers, the present thesis analyses results for two cohorts of patients treated for early-stage cHL with combined modality. The cohorts are population-based and have been treated with radiation fields that are reduced compared with fields used in earlier population-based cohorts.

The cohorts exhibit excess morbidity, hazard ratio (HR) 1.6 (95% Confidence Interval, CI, 1.1–2.4) for second cancers, HR 1.4 (95%CI, 1.1–1.8) for diseases of the circulatory system, and HR 2.6 (95%CI, 1.6–4.3) for diseases of the respiratory system. The first cohort, diagnosed 1999–2005, does not deviate from expected survival in the general population. The only subgroup analysed with excess mortality consists of patients with progressive cHL within 5 years of follow-up. The later cohort, patients diagnosed 2006–2015, exhibits a small but statistically significant excess mortality, relative survival rate 0.97 (95%CI, 0.95–0.99) at 10 years of follow-up. In analyses of years of life lost according to cause of death, second malignancies are the leading cause of death, 1.17 years/patient compared with 0.41 years/comparator ($p=0.004$) in the first cohort. Progressive cHL is the dominating cause of death in the second cohort.

In these two cohorts with early-stage cHL treated with combined modality, excess morbidity exists, but on a much lower level than in previously published population-based cohorts, which reported standardised incidence ratios of 4–5 for second cancers and 4–7 for cardiovascular disease. Survival is excellent with only marginal or no excess mortality compared with the general population. The excess mortality in the second cohort is almost certainly caused by deaths due to progressive cHL.

In conclusion, the substantial reduction in excess morbidity from treatment toxicity result in no, or minimal excess mortality. The cause of death that can be correlated to any significant excess mortality is progressive cHL. These results argue in favour of continuing to strive for disease control, suggesting that, at present, combined modality should be used to treat early-stage cHL.

Keywords: Hodgkin lymphoma, combined modality, late effects, treatment toxicity, radiotherapy, chemotherapy, long-term, follow-up, relative survival, years of life lost, excess mortality, excess morbidity

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To Karin, Elsa and Emil.

List of Papers

This thesis is based on the following papers.

- I. **Lagerlöf, I**, Holte, H, Glimelius, I, Björkholm, M, Enblad, G, Erlanson, M, Fluge, Ø, Fohlin, H, Fosså, A, Goldkuhl, C, Gustavsson, A, Johansson, A-S, Linderöth, J, Nome, O, Palma, M, Åkesson, L, Østenstad, B, Raud, C, Glimelius, B, Molin, D. (2020)
No excess long-term mortality in stage I-IIA Hodgkin lymphoma patients treated with ABVD and limited field radiotherapy.
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- II. **Lagerlöf, I**, Fohlin, H, Enblad, G, Glimelius, B, Goldkuhl, C, Palma, M, Åkesson, L, Glimelius, I, Molin, D. (2022)
Limited, But Not Eliminated, Excess Long-Term Morbidity in Stage I-IIA Hodgkin Lymphoma Treated with Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Limited-Field Radiotherapy.
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- III. **Lagerlöf, I**, Fohlin, H, Enblad, G, Glimelius, B, Goldkuhl, C, Palma, M, Glimelius, I, Molin, D.
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- IV. **Lagerlöf, I**, Wikman, P, Fohlin, H, Enblad, G, Glimelius, B, Goldkuhl, C, Palma, M, Glimelius, I, Molin, D.
Real-life data on morbidity and cause-specific mortality after combined modality treatment for Hodgkin lymphoma 2006-2015. *In manuscript*

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Related Papers

- Andersson, A, Enblad, G, Tavelin, B, Björkholm, M, Linderoth, J, **Lagerlöf, I**, Merup, M, Sender, M, Malmer, B. (2008) **Family history of cancer as a risk factor for second malignancies after Hodgkin's lymphoma.** *Br J Cancer*, 98(5): 1001–1005
- Jakobsen, LH, Ellin, F, Smeland, KB, Wästerlid, T, Christensen, JH, Jørgensen, JM, Josefsson, PL, Øvlisen, AK, Holte, H, Blaker, YN, Grauslund, JH, Bjørn, J, Molin, D, **Lagerlöf, I**, Smedby, KE, Colvin, K, Thanarajasingam, G, Maurer, MJ, Habermann, TM, Song, KW, Zhu, KY, Gerrie, AS, Cheah, CY, El-Galaly, TC. (2020) **Minimal relapse risk and early normalization of survival for patients with Burkitt lymphoma treated with intensive immunochemotherapy: an international study of 264 real-world patients.** *Br J Haematol* 189(4):661-671
- Harwood, M, Hodges, G, Tan, X, Cheah, CY, Lim, K, Ku, M, Tam, C, **Lagerlof, I**, Cochrane, T. (2020) **Characteristics and outcome of patients with relapsed/refractory Hodgkin lymphoma following front-line escalated BEACOPP-based chemotherapy: a report from the Australasian Lymphoma Alliance.** *Leuk Lymphoma* 61(14):3412-3416
- Wahlin, BE, Övergaard, N, Peterson, S, Digkas, E, Glimelius, I, **Lagerlöf, I**, Johansson, AS, Palma, M, Hansson, L, Linderoth, J, Goldkuhl, C, Molin, D. (2021) **Real-world data on treatment concepts in classical Hodgkin lymphoma in Sweden 2000-2014, focusing on patients aged >60 years.** *EJHaem* 2(3):400-412
- Fjordén, K, Ekberg, S, Kuric, N, Smedby, K, **Lagerlöf, I**, Larsen, T, Jørgensen, J, de Nully Brown, P, Jerkeman, M. (2022) **Idelalisib in relapsed/refractory diffuse large B-cell lymphoma: results from a Nordic Lymphoma Group phase II trial.** *Br J Haematol* 196(2):437-440

Contents

Introduction.....	11
Aims.....	12
Background.....	13
Epidemiology.....	13
Aetiology.....	13
The tumour cell and the tumour microenvironment.....	14
Clinical features.....	15
Clinical investigations, prognosis, and predictive factors.....	16
Treatment.....	19
History of treatment.....	19
Evolution of radiotherapy.....	21
Current clinical practise in treatment of early-stage cHL.....	24
Treatment-related morbidity and mortality.....	26
Second cancer.....	26
Diseases of the circulatory system.....	26
Diseases of the respiratory system.....	27
Patients and methods.....	28
Use of registers in the studies.....	28
The Nordic Register.....	28
The Swedish national registers.....	28
Linkage.....	29
Statistical analyses.....	30
Ethical considerations.....	31
Results.....	32
Main findings.....	32
Paper I.....	32
Paper II.....	34
Paper III.....	35
Paper IV.....	36
Discussion and conclusions.....	38
Future perspective.....	40

Sammanfattning på svenska.....	41
Bakgrund	41
Målsättning och metoder	41
Delarbete I	42
Delarbete II	42
Delarbete III.....	42
Delarbete IV	43
Slutsatser.....	43
References.....	47

Abbreviations

2D	two-dimensional
3D	three-dimensional
5-PS	five-point scale
ABVD	doxorubicin, bleomycin, vinblastine and dacarbazine
A-AVD	brentuximab vedotin-doxorubicin, vinblastine and dacarbazine
AVD	doxorubicin, vinblastine and dacarbazine
N-AVD	nivolumab-doxorubicin, vinblastine and dacarbazine
BEACOPPesc	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone in escalated dose
BrECADD	brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone
Ca	cancer
CD	cluster of differentiation
cHL	classical Hodgkin lymphoma
CI	confidence interval
CT	computerized tomography
DCS	diseases of the circulatory system
DRS	diseases of the respiratory system
EBV	Epstein-Barr virus
EORTC	European organisation for research and treatment of cancer
FDG-PET/CT	fluorodeoxyglucose -positron emission tomography/computerised tomography
GHSg	German Hodgkin study group
Gy	Gray
HIV	human immunodeficiency virus
HR	hazard ratio
HRS	Hodgkin/Reed-Sternberg
IMRT	intensity-modulated radiation therapy
IPS	international prognostic score
IQR	interquartile range
LYSA	the Lymphoma study association
MOPP	vincristine sulphate, nitrogen mustard (or cyclophosphamide), procarbazine hydrochloride, and prednisone
NCI	National cancer institute
NLG	Nordic lymphoma group

NOS	not otherwise specified
PET	positron emission tomography
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
RS	relative survival
RSR	relative survival rate
SIR	standardised incidence ratio
SMR	standardised mortality ratio
TTP	time to progression
VMAT	volumetric modulated arc therapy
WHO	World health organization

Introduction

Measuring survival in a cohort entails measuring the time and frequency of death. This may be straight forward when measuring the impact of an exposure that carries a substantial risk of death in the near future, but is harder when the risk is spread over a long time. Moreover, is survival, measured in years, an adequate endpoint for successful treatment? When analysing long-term survival in mortals, is death at some point acceptable? Or does all death, irrespective of when it occurs in an individual life, have the same weight?

This thesis studies the long-term influence of classical Hodgkin lymphoma (cHL), and its treatment, on morbidity and survival. Toxicity from treatment is known to occur over decades, primarily in the form of excess malignancies, cardiovascular disease and lung injuries, all of which impact survival. As malignancies and cardiovascular disease also heavily impacts morbidity and survival in the general population, a suitable control group is essential to be able to accurately calculate the effect of exposure.

With mortality from cHL diminishing during the past 50 years, greater weight is given to treatment toxicity when choosing first line treatment. In these decisions, both for individual patients and in designing clinical trials, one trend is to reduce long-term treatment toxicity by accepting a certain loss of disease control. When deciding on this balance, temporal issues with the scale need to be addressed. The weight of treatment toxicity is assessed in relation to treatment techniques used several decades ago, whereas results related to disease control are much more contemporary. Mirroring this problem, it is difficult to estimate the impact of excess malignancies and cardiovascular disease occurring several decades in the future, as healthcare can be assumed to improve over time.

Radiotherapy used for cHL, has been shown to contribute substantially to late toxicity. Yet it is also a modality that has changed greatly over time with respect to definitions of fields and techniques of delivery, thereby potentially mitigating its adverse effects. The studies in this thesis contribute information about such toxicity in patients treated with more modern principles of radiotherapy.

Aims

The aim of this thesis is to quantify the impact of close to modern combined modality treatment for early-stage cHL, among adults, on morbidity and mortality, by linking lymphoma registers with health registers.

More specifically to:

- Ascertain long-term results for cHL-patients, treated in first line with combined modality, where the radiotherapy is given according to a precisely-defined protocol with fields more limited than the *involved field*.
- Use long-term relative survival (i.e., excess mortality) as a measure of treatment toxicity.
- Compare risk of death from cHL to risk of death from treatment related morbidities.
- Determine excess morbidity from second cancers, cardiovascular disease, and pulmonary disease using matched comparators.
- Compare levels of excess morbidity in these cHL-patients with levels in earlier published cohorts.

Background

Epidemiology

Hodgkin lymphoma was first described in 1832 by Thomas Hodgkin¹. It is a lymphoid malignancy that can be divided into classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma, based on the immunophenotype and morphology². Nodular lymphocyte predominant Hodgkin lymphoma is an altogether separate entity and is not the subject of this thesis. Classical Hodgkin lymphoma accounts for about 90% of all diagnoses of the malignancy, and has a bimodal age distribution with peak incidences at the age of approximately 20 and 75 years^{3,4}. The incidence of other lymphoma entities has increased in recent decades⁵. However, cHL is an exception with crude annual incidence rates in Europe per 100 000 population remaining at 2.7 and 2.1 for males and females respectively⁶. Incidence in the Nordic countries (pooled) is 2.25 and 1.66 for males and females respectively⁷. The sibling of a patient diagnosed with cHL has a standardised incidence ratio (SIR) of 6 to develop cHL; for same sex twins, the SIR is 57^{8,9}. Familial aggregation of cHL can be the result of shared environmental factors as well as genetic susceptibility¹⁰.

Aetiology

Early hypotheses maintained that the bimodal age distribution of Hodgkin lymphoma indicated a difference in aetiology for the respective peak, and that an infectious agent was the cause of the early peak^{3,11}. Reported correlation of the risk of cHL during the early peak and socioeconomic affluence (i.e. correlation to good sanitation and good hygiene conditions) during childhood suggested that delayed childhood infections were of importance. Infectious mononucleosis, caused by a late (i.e. during adolescence) Epstein-Barr virus (EBV) infection, was found to increase the risk of Hodgkin lymphoma¹². The finding was replicated¹³ but was later found to correlate only with cHL where EBV can be found in the tumour cell^{14,15}. In the developed world, the prevalence of EBV in the tumour cell of cHL varies (10–75%) according to histological subtype¹⁶. In developing countries, and in particular in paediatric patients and HIV-associated cHL, the prevalence of EBV is much higher, reaching up to 100%¹⁷. Thus, EBV has been found to play a role in the pathogenesis

of cHL, but only in some cases. No other infectious agent has yet been implicated. In genome-wide studies, several risk loci for genetic susceptibility have been identified, several of them known to predispose for immune dysfunction¹⁰.

The tumour cell and the tumour microenvironment

The Hodgkin/Reed-Sternberg (HRS) cell is the neoplastic cell of cHL, first described by Carl Sternberg¹⁸. Dorothy Reed then further characterised the cell, while refuting the theory that it was a result of tuberculosis¹⁹. Typical HRS cells are large with at least two nuclear lobes or nuclei and a slightly basophilic cytoplasm (Figure 1). Other variants, such as mononuclear cells, named Hodgkin cells, or cells with condensed cytoplasm, called mummified cells, can be present with or without HRS cells. The normal counterpart to the neoplastic cell is almost always the germinal centre derived B-cell²⁰. In rare cases the neoplastic cell is derived from a T cell²¹.

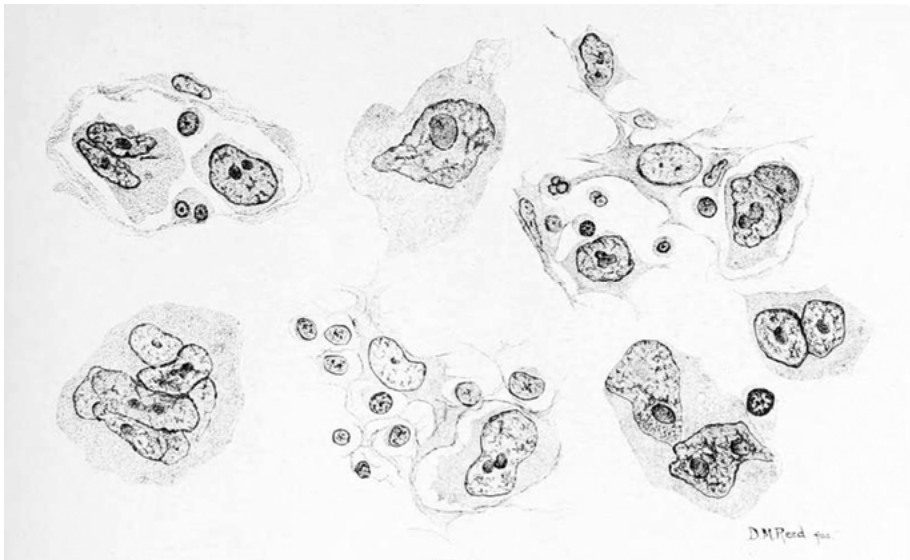


Figure 1. Hodgkin Reed-Sternberg (HRS) cells depicted by Dorothy Reed. Reed D. 1902: 196 Plate VII Fig 4; Johns Hopkins Hospital Report 1902; 10: 113–196.

The neoplastic HRS cells constitute a minority (0.1–10%) of the cells in the tumour and appear against a background of reactive cells (small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells and mast cells), called by-stander cells. These cells do not constitute a proper immune response to the HRS cells but are part of the necessary environment for the survival of the

neoplastic cell²². An area on the short arm of chromosome 9 (9p24.1) of the HRS cell has been shown to be abnormal (polysomy, copy-number gain, or amplification) in almost all cases of cHL^{23,24}. This results in an overexpression of programmed death-ligands 1 and 2 (PD-L1 and PD-L2) on the surface of HRS cells²⁴. The physiological function of interaction between cells through PD-L1 and PD-L2 and their counterpart on T cells, programmed cell-death protein 1 (PD-1), is inhibition of an immune response^{25,26}. This constitutes an important mechanism to constrain autoreactive T cells²⁷. Through this mechanism, neoplastic cells can communicate with T cells through PD-L1 and PD-L2 expressed on the cell surface to achieve immune evasion²⁸.

Traditionally cHL has been classified into four subtypes, nodular-sclerosis, mixed-cellularity, lymphocyte-rich and lymphocyte-depleted. The differentiation mainly arises from the composition of the bystander cells and to some extent the characteristics of the HRS cells. Subtypes differ in EBV prevalence, age distribution and clinical presentation, which suggests differences in the underlying biology and pathology. If technical issues prevent the diagnosis of the subtype, a diagnosis of cHL not otherwise specified (NOS) is sufficient. With the treatment used at present, diagnosis of the subtype gives no predictive information.

Clinical features

Classical Hodgkin lymphoma often presents as an enlargement of peripheral lymph nodes, most often in the cervical region (75%). After cervical involvement, the most common site is the mediastinum followed by axillar and para-aortic regions. Engagement of the spleen is common (20%), whereas extranodal spread is uncommon. Bone marrow involvement (5%) represents a dissemination of the neoplastic cell by circulating blood. In some patients (40%), the enlargement is accompanied by constitutional symptoms, fever, drenching night sweats and weight loss, called B-symptoms². If the spread of cHL does not include palpable lymph node regions the symptoms might be indirect, such as respiratory or circulatory signs, caused by compression of organs or vessels due to tumour progression. Chronic pruritus is reported in up to 19% of patients with cHL²⁹. An underreported symptom of cHL is alcohol intolerance, most often described as pain directly following intake of alcohol. In interviews with consecutive patients with cHL, the incidence of alcohol intolerance was 45% among persons with regular alcohol intake³⁰ (published in the 1960s). In the modern era this seems to be much more uncommon³¹.

Clinical investigations, prognosis, and predictive factors

When investigating suspected cHL the tissue sample from the tumour is central to diagnosis. As the neoplastic cells constitute a minority of cells in the tumour, and the diagnosis also relies on the architecture of bystander cells, fine-needle aspirates cannot be used. Although surgical biopsies are preferred, core biopsies, with guidance from ultrasound, are often used in more complicated locations. If involvement is restricted to the mediastinum, the use of mediastinoscopy might be needed to obtain a tissue sample. Fluorodeoxyglucose-positron emission tomography/computerised tomography (FDG-PET/CT) is currently used to determine the spread of the disease. This medical imaging technique combines a conventional CT with FDG-PET, to map the intensity of glucose metabolism. By infusing FDG (^{18}F) before the imaging procedure, the three-dimensional distribution of FDG in the patient can be detected by sensors picking up the radioactive decay of ^{18}F , and correlate it in images to structures defined by the CT. As the tumours in cHL have markedly greater metabolism of FDG, than normal tissue, sensitivity to detecting involvement is increased. This is especially true in early lesions where lymph nodes are not yet visibly enlarged or in locations, if involved, that do not change appearance on CT, such as the bone marrow³².

Table 1. Stage according to Ann Arbor 1971. Originally differentiating between on the one hand pathological stage, i.e., stage that were supported by tissue samples such as diagnostic splenectomy, bone marrow or liver biopsy and on the other hand clinical stage supported by clinical examination and medical imaging. Revised at Cotswold 1989.

Stage	Definition:
I	Involvement of one single lymph node region or one single extralymphatic site.
II	Involvement of more than one region, or one region and local extra lymphatic involvement but restricted to one side of the diaphragm.
III	Involvement on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic sites
Further characterization of disease stage:	
A or B	A: no B-symptoms B: at least one B-symptom (unexplained fever, unexplained weight loss >10%, or drenching night sweats)
E	Single extralymphatic or local extralymphatic involvement
X	Bulky tumour: >1/3 of intra thoracic diameter at the level of thoracic vertebrae 5/6. In Sweden, since 1999, also including >10cm diameter on computerized tomography.

Whereas the techniques for determining the extent of the disease have changed over the years, the extent itself has consistently been defined by stage according to the Ann Arbor classification³³ and modifications in Cotswold³⁴. This classification has four stages of disease with additional information regarding presence of B-symptoms, single extranodal involvement and bulky disease (Table 1). Early stage is generally defined as Stages I and II, and often includes some of the patients with B-symptoms. Advanced stage disease is defined as stage IIB, III and IV.

Clinical risk factors used today, before starting of first-line treatment, were first introduced two decades ago. For advanced stage cHL the international prognostic score (IPS) was published in 1998³⁵. The IPS consists of seven risk factors (serum albumin<40g/L, blood haemoglobin <105g/L, male sex, age>44years, stage IV, white blood cell count>15x10⁹/L, lymphocyte count <0.6/L or <8% of white blood cell count). The presence of more than two factors is generally perceived as high risk. Initial treatment for advanced stage cHL, according to current national guidelines in Sweden, is uniform and does not differ according to IPS.

For early-stage cHL, the risk factors used in Sweden today were introduced in the HD10 study that commenced inclusion in 1998³⁶. In an adaptation to clinical tradition in Sweden, national guidelines define early-stage as stage I-IIA. Three risk factors (involvement of more than two lymph node regions, erythrocyte sedimentation rate >50mm, and bulky disease) are used to decide the number of cycles of chemotherapy and the dose of radiotherapy in the first line of treatment. It is important to note that the definition of the extent of disease that constitutes an adverse prognostic factor is not the same in Sweden, the German Hodgkin Study Group (GHSg)³⁶, and the European Organisation for Research and Treatment of Cancer (EORTC)³⁷, for example. Thus, a small proportion of patients might be classified differently in respect of early stage or advanced stage, with favourable or unfavourable prognosis, depending on geography (Table 3).

Table 2. Deauville score, also called 5-point scale (5-PS)^{38,39}

Deauville score	
1	No FDG-uptake
2	FDG-uptake ≤ mediastinal blood pool
3	FDG-uptake >mediastinal blood pool but ≤ normal liver
4	Moderately above FDG-uptake of normal liver
5	Markedly above FDG-uptake of normal liver or new sites

The strongest predictor of treatment outcome to date is early assessment with FDG-PET/CT, typically after two cycles of chemotherapy, first described in advanced stage disease^{40,41} and then in early-stage disease⁴², in the latter case with less specificity, but with maintained negative predictive value. Early interim FDG-PET/CT measures the dynamic effect of treatment on tumour metabolism. To improve the level of interobserver agreement, a five-point scale was developed (Table 2), where the intensity of FDG uptake in cHL-tumours was related to the uptake in the mediastinal blood pool and normal liver^{38,39}. The five-point scale, called the Deauville score, has two thresholds for a positive FDG-PET/CT. One is above the mediastinal blood pool uptake, for high sensitivity; the other above the liver uptake, for high specificity. At present, the threshold for the liver is almost always used as a cut-off for a positive scan in clinical practice and clinical trials.

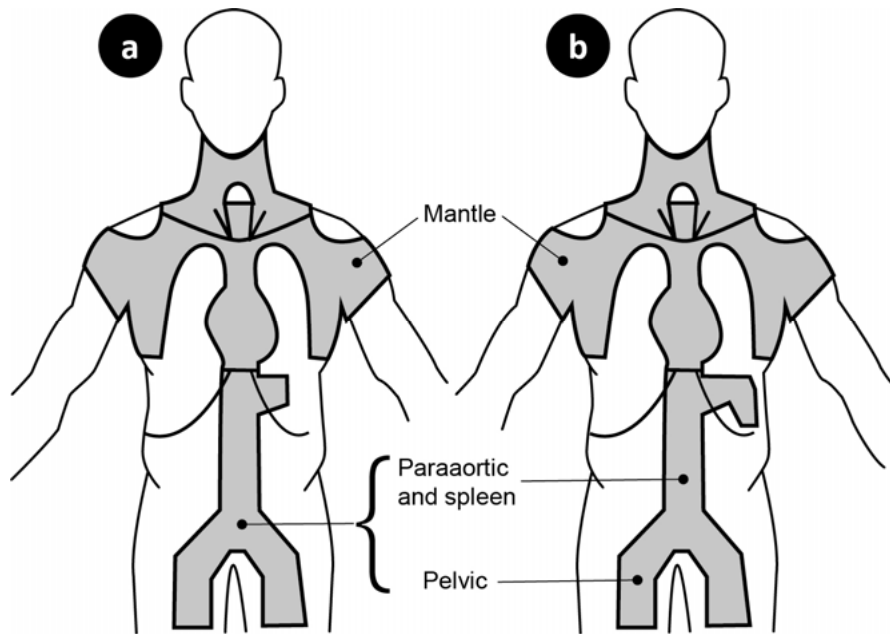


Figure 2. Mantle field together with Inverted Y field for total-lymphoid irradiation (i.e., an example of extended field irradiation).

a) Two field technique. b) Three field technique, used when spleen is still present.

Rosenberg S.A. and Kaplan H.S. 1970⁴³

Treatment

History of treatment

Classical Hodgkin lymphoma that remains untreated, almost invariably results in death⁴⁴. The treatment modality that first resulted in a cure was radiotherapy, primarily used for localised disease⁴⁴. Increasing dose and size of fields, such as the mantle field and the inverted-Y field that could be combined for total-lymphoid irradiation (Figure 2), enabled the successful treatment of more advanced disease. This resulted in a major gain in relapse free survival⁴³. Chemotherapy was successfully added to radiotherapy (i.e. combined modality treatment) for long-term disease control in the H1-study by the EORTC, where weekly dosing of vinblastine for two years after radiotherapy lifted relapse-free survival at 15 years from 38% to 60%⁴⁵. Combination chemotherapy was first used in the relapse setting and then successfully in first-line treatment in advanced stage disease. Vincristine sulphate, nitrogen mustard (or cyclophosphamide), procarbazine hydrochloride, and prednisone (MOPP) given in cycles for a total of six months achieved an overall survival at four years of 63% in first-line treatment of advanced stage cHL⁴⁶. MOPP was replaced by doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) when the later

were shown to be more effective and less toxic⁴⁷. The combination of MOPP and ABVD administered before radiotherapy was used during the late 1980s and early 1990s in Sweden. In a retrospective study it was shown to be superior to radiotherapy alone⁴⁸. Two cycles of ABVD preceding extended field radiotherapy in the HD7-study, by the GHSG, resulted in significantly better disease control than radiotherapy alone⁴⁹.

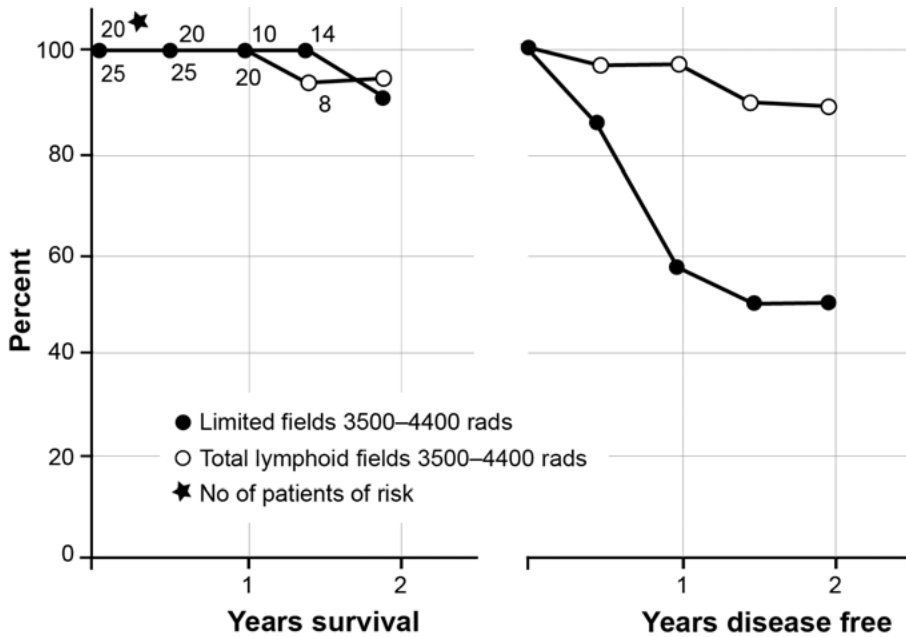


Figure 3. Results of a randomised trial of total-lymphoid irradiation compared with limited field. Cumulative proportion surviving, and number at risk to the left. Cumulative proportion disease-free to the right. One rad is equal to 0.01 Gray. Rosenberg S.A. and Kaplan H.S. 1970⁴³

By this point, the number of patients experiencing long-term survival had increased and the problem of serious long-term toxicity was becoming apparent. In retrospective studies treatment toxicity was shown to be strongly correlated to the dose and the size of the field of radiotherapy^{50,51}. Thus, most subsequent clinical trials were designed to reduce dose and size of field while retaining the high level of long-term disease control. In advanced disease, radiotherapy quickly lost in importance, being replaced by combination chemotherapy, and used only for local control of residual disease. In parts of the world, the combination bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone in escalated dose (BEACOPPesc) has been adopted. It is a more intense chemotherapy combination than ABVD and has been shown to achieve superior disease control⁵²⁻⁵⁴. One later addition to treating cHL is the antibody drug conjugate brentuximab vedotin, consisting of the

antibody brentuximab, aimed at the cell surface antigen CD30, and the cytotoxic substance vedotin. Through several randomised clinical trials, the drug is now incorporated into the first line of treatment for advanced stage cHL in two different combinations. One entails adding brentuximab vedotin to AVD (i.e. ABVD without bleomycin) named A-AVD⁵⁵. The other adds brentuximab vedotin to a modification of BEACOPPesc; brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone (BrECADD) with impressive results concerning disease control, with progression-free survival of 94.9% after three years of follow-up⁵⁶. No randomised trials exist to incorporate brentuximab vedotin in the treatment of early stage cHL. The latest addition of importance to the treatment of cHL is immune checkpoint inhibitors, primarily the PD1 -inhibitors nivolumab and pembrolizumab, both of which shows powerful single agent effect in the relapsed/refractory setting⁵⁷. An ongoing randomised trial in first-line treatment of advanced stage disease combines nivolumab with AVD (N-AVD). Results are very promising, with progression-free survival of 94%, but with a median follow-up of only 12 months⁵⁸.

Evolution of radiotherapy

Whereas some patients with localised disease could be saved with early radiation therapy, large radiation fields such as total or subtotal nodal irradiation constituted the real breakthrough in treating cHL. In a clinical trial (1962–1970), of cHL, Stages I–IIA, randomising between limited radiotherapy and total nodal irradiation (Figure 2), 50% and 90% respectively were continuously disease-free after two years⁴³ (Figure 3). This treatment involved radiation doses of 35–44 Gray (Gy) given in 2 Gy fractions and delivered as two opposing fields.

Incorporating the use of CT enabled a more accurate determination of the extent of lymphoma involvement and more exact reference points to for the radiation fields. This resulted in the gradual development of the concept of three-dimensional conformal radiation therapy.

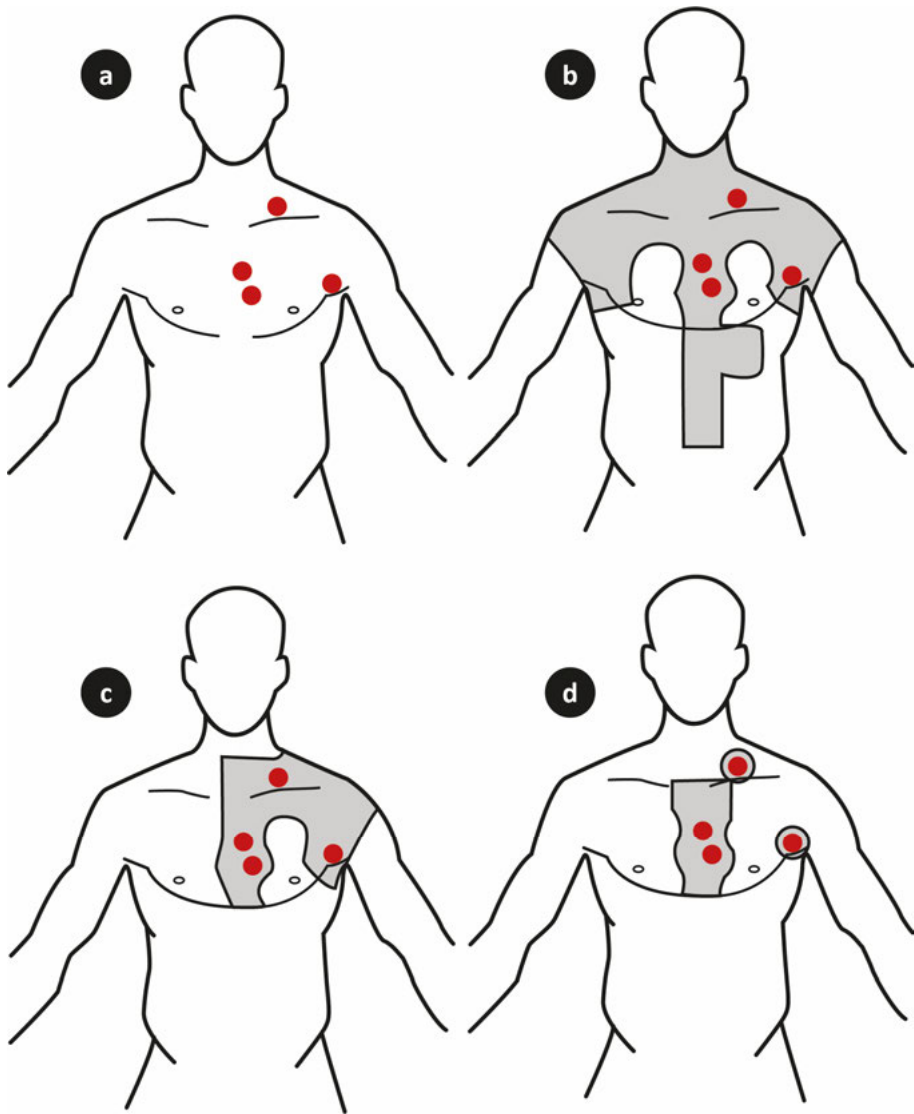


Figure 4. Stepwise change of radiotherapy fields for classical Hodgkin lymphoma. Involved lymph nodes in red. Extent of respective field in grey. a) Involved lymph nodes. b) Mantle field (Extended field). c) Involved field. d) Involved node.
 Witkowska M et al. 2015⁵⁹

Motivated by extensive long-term toxicity from the use of large fields and high doses these technical gains enabled the fields to be shrunk and doses to be reduced. Through several randomised clinical trials, field size was reduced using the concepts of involved field followed by involved node, and involved site^{36,60-62} (Figures 4 and 5). In parallel the radiotherapy dose was gradually

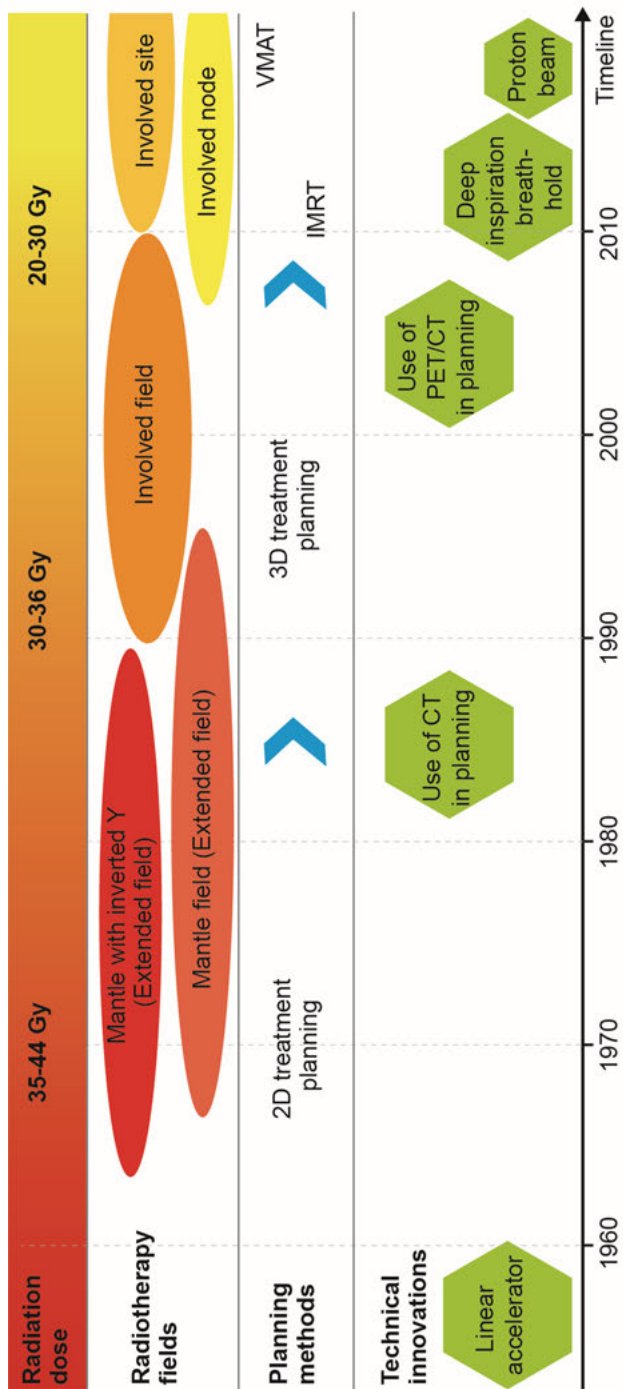


Figure 5. Evolution of radiotherapy for classical Hodgkin lymphoma. Approximations of changes according to a timeline (bottom). Starting from the top, showing changes in; radiation dose, radiotherapy fields, planning methods and technical innovations.

Abbreviations: Gy: Gray. 2D: two-dimensional. 3D: three-dimensional. IMRT: intensity-modulated radiation therapy. VMAT: volumetric modulated arc therapy. CT: computerised tomography. PET: positron emission tomography.

reduced to the currently widely used level of 20Gy, or 30 Gy in the presence of risk factors³⁶ (Figure 5).

Current clinical practise in treatment of early-stage cHL

Recent large randomised trials in early-stage cHL have aimed to exclude radiotherapy in patients that are PET-negative after often brief combination chemotherapy. These trials (RAPID, H10, HD16, and HD17) were all designed for non-inferiority in this respect, and all except the HD17 were negative^{61,63-65}. The exception, HD17, included only patients with unfavourable (prognosis) early-stage cHL and included initially very intensive chemotherapy after which 2/3 of patients were able to avoid radiotherapy without substantial loss of disease control. In the other trials, relapse risk was at least doubled (95%CI) unless chemotherapy was significantly increased compared with the standard arm. With the available follow-up time, no statistically significant difference exist in overall survival in any of the trials. These results have been interpreted differently in different parts of the world. In many parts of Europe combined modality remains the first choice for treatment of early-stage disease³⁷ whereas the addition of radiotherapy is considered optional in the United States, and the more frequently used alternative is chemotherapy only⁶⁶ (Table 3).

Table 3. Current guidelines for treatment of early-stage classical Hodgkin lymphoma in different areas of Europe (Sweden, German Hodgkin study group, European organisation for research and treatment of cancer, the Lymphoma study association) and the United States (National cancer institute).

Location/study group	Sweden	Europe GHSG	Europe EORTC/LYSA	The United States NCI
Prognostic group	Without risk factors	Limited stage	Limited stage	Favorable
Treatment	With risk factors ¹	Intermediate stage ²	Intermediate stage ³	Unfavorable ⁴
	ABVD x2 + 20 Gy ISRT/INRT	ABVD x2 + 20Gy ISRT/INRT	ABVD x2 → PET/CT	ABVD x2 + 20Gy ISRT/INRT
	ABVD x4+ 30Gy ISRT/INRT	ABVD x4 + 30Gy ISRT/INRT	PET- → ABVD x1 + 20Gy ISRT/INRT	ABVD x4 +20-30Gy ISRT/INRT
	or	or	PET- → ABVD x2 +30Gy ISRT/INRT	or
	BEACOPPesc x2 + ABVD x2 → PET/CT	BEACOPPesc x2 + 30Gy ISRT/INRT	PET+ → BEACOPPesc x2 + 30Gy ISRT/INRT	ABVD x2 → PET/CT
	PET- → EOT			PET- → ABVD x1-2
	PET+ → 30Gy ISRT/INRT			PET+ → A-AVD x4 or BEACOPPesc x4

Abbreviation: GHSG: German Hodgkin Study Group. EORTC: European Organisation for Research and Treatment of Cancer. LYSA: The Lymphoma Study Association. NCI: National Cancer Institute. ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine. Gy: Gray. ISRT: involved site radiotherapy.

INRT: involved node radiotherapy. BEACOPPesc: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone in escalated dose. PET/CT: positron emission tomography/computerized tomography. A-AVD: brentuximab vedotin-doxorubicin, vinblastine, dacarbazine.

¹ ≥1 risk factor: ESR>50mm, bulky tumour (>10cm any diameter or 1/3 of intrathoracic diameter), >2 involved lymph node regions according to Ann Arbor. Stage IIB is defined as advanced disease.

² ≥1 risk factor: ESR≥50mm or ≥30mm with B-symptoms, large mediastinal tumour (≥1/3 of intrathoracic diameter), >2 involved lymph node areas according to GHSG, extranodal disease. Stage IIB together with large mediastinal mass or extranodal disease is defined as advanced disease.

³ ≥1 risk factor: ESR≥50mm or ≥30mm with B-symptoms, large mediastinal tumour (≥0.35 of intrathoracic diameter), >3 involved lymph node areas according to EORTC, Age≥50 years.

⁴ ≥1 risk factor: ESR>50mm, bulky tumour (>10cm any diameter or 1/3 of intrathoracic diameter), >2 involved lymph node regions according to Ann Arbor, extranodal disease, B-symptoms.

Treatment-related morbidity and mortality

Second cancer

As new treatment concepts achieved long-term survival, it was clear early on that success came at a price. Survivors of cHL have been shown to experience increased levels of malignancies such as acute leukaemia, breast cancer and lung cancer^{50,67-71}. Often, the increased risk is measured by grouping all malignancies as “any malignancy”. The increased risk of acute leukaemia among Hodgkin lymphoma survivors could clearly be correlated to alkylating chemotherapy and was observed to be reduced when less toxic chemotherapy combinations were introduced⁶⁷. Increased risk of any malignancy among survivors of cHL has been shown to be correlated to the extent of radiotherapy field and radiation dose^{50,72}. In the study with the longest follow-up, to date, the SIR for any malignancy is 4.6 (95%CI, 4.3–4.9) starting 5 years after diagnosis of cHL and remaining relatively unchanged during 40 years of follow-up⁵⁰. The risk of any malignancy did not appear to change according to treatment period, including patients diagnosed up to the turn of the millennium. Although no significant reduction in SIR for any malignancy, or more specifically for breast cancer, has been seen in more modern treatment periods, the risk of breast cancer is less, when less extensive radiotherapy fields are used⁶⁸. The relative risk of developing any malignancy has been shown to be higher in patients treated for cHL at a younger age⁷².

The excess malignancies among cHL survivors have been shown to result in excess mortality, with a standardised mortality ratio of approximately 5 to 6⁷³⁻⁷⁵.

Diseases of the circulatory system

Survivors of cHL have an increased risk of cardiovascular disease compared with the general population⁷⁶⁻⁷⁸. Patients treated according to different radiotherapy concepts, chemotherapy combinations and combined modality have been found to have a long-term elevated risk of coronary heart disease, heart failure, valvular heart disease, cerebrovascular disease, and hypertension⁷⁶⁻⁸⁰. This reflects the cardiovascular toxicity of several components of chemotherapy and radiotherapy that include cardiovascular structures in the treatment field⁷⁸⁻⁸⁰. Among chemotherapy agents used, heart failure from anthracyclines is well described, with the risk related to cumulative dose⁷⁹. In a large retrospective study, including patients treated until the mid-1990s in the Netherlands, SIR for an event of either coronary heart disease or heart failure persisted at 4 to 7, with patients treated at a younger age (<25 years) at the higher end. The excess risk of diseases of the circulatory system has not decreased significantly in the later part of the period studied^{78,80}.

The excess risk of cardiovascular disease has resulted in increased levels of cardiovascular mortality^{73,74,81}. In the Dutch cohort, SMR for diseases of the circulatory system is 5.5⁷⁵. Excess mortality caused by cardiovascular disease, is lower among patients treated during the latter part of the period⁷⁵.

Diseases of the respiratory system

Chemotherapy agents used in the treatment of cHL have potential pulmonary toxicity^{82,83}. Bleomycin has the largest risk of severe, potentially deadly, pulmonary toxicity⁸² with the risk increasing with higher cumulative dose and higher age⁸⁴. In a randomised study, the risk of a bleomycin induced pneumonitis as well as for a reduction of the pulmonary diffusing capacity were increased with a higher cumulative dose of bleomycin⁸⁵. Radiotherapy in which the field involves parts of the lungs carries the risk of radiation induced lung injury⁸⁶. Several reports describe therapy-induced lung injuries in cHL-patients, but follow-up is often short, seldom longer than two years^{82,87,88}.

Patients and methods

Use of registers in the studies

The Nordic Register

Through the Nordic lymphoma group (NLG), national guidelines for treatment of early-stage cHL in Sweden and Norway were updated and harmonised in 1999. Early-stage was defined as stage IA and IIA. Disease stage was determined using CT, chest X-ray, abdominal ultrasound, and bone marrow biopsy. Bulky disease was defined as a tumour diameter of ≥ 10 cm in any direction or ≥ 0.33 of the intra-thoracic diameter at the Th 5–6 level on a posterior anterior chest X-ray. Preferred treatment was two cycles of ABVD followed by 30 Gy radiotherapy with the option of an additional 5 Gy boost to the tumour bed. In the presence of at least one risk factor (ESR > 50 mm, bulky disease, involvement of > 2 lymph node regions) chemotherapy was increased to four cycles of ABVD. These risk factors were implemented in the HD10 study³⁶, but not published at that time. The most important change in the guidelines was a significant reduction of field size for radiotherapy, characterised as a modification of involved field. This modification included an intention not to treat the entire lymph node region in the instance of limited involvement of that region, allowing instead a margin of approximately three centimetres (depending on orientation and locale). Earlier use of such limited fields on a population-based level has not been reported. Guidelines allowed for the use of full chemotherapy without radiotherapy if the treatment field was deemed unacceptable. Alternative chemotherapy as well as radiotherapy only were allowed for elderly and frail patients. To monitor compliance with the guidelines, national registers for early-stage cHL were introduced in both countries. The individual clinician reported disease characteristics, planned treatment, treatment results and follow-up. The guidelines were implemented in 1999 and remained in use without relevant change until 2005.

The Swedish national registers

The Swedish Lymphoma Register

Since 2000 all types of malignant lymphoma with extent of disease and prognostic factors are included. As of 2007 the register includes information on

primary treatment and treatment results. In 2010, information on lymphoma relapse was added.

The National Cancer Register

Since 1958, the National Cancer Register, contain information on all types of malignancies. As all new cases of a malignancy have to be reported the register is above 95% complete⁸⁹. The register contains information on the basis for and date of diagnosis, site of tumour and histological subtype.

The National Patient Register

During the 1960s data on inpatient care began to be collected, but not from all of Sweden and not across all areas of care. In 1984, participation became mandatory for all care givers and since 1987 all inpatient care is reported. Outpatient visits to physicians have been reported since 2001. Primary care is not included. Information includes date of visit or dates of inpatient care, primary and secondary diagnosis and, where applicable, external causes and procedures.

The National Cause of Death Register

Reporting on population statistics, including cause of death, has been comprehensive since 1747 in Sweden. The current database, with classifications according to standards from the World Health Organization (WHO), covers the time from 1952 to the present. The register lacks information on less than two percent of deaths.

The Total Population Register

Data reported by the Swedish Tax Agency provides longitudinal cover for, age, sex, and residency, among other things, from birth (or immigration) until death (or emigration). This register can be used to recruit matched comparators.

Linkage

Laws and procedure

Data in the registers used is protected by absolute confidentiality according to Swedish law, to which there are a few exceptions. One such is extraction of data for research. Given approval from the Swedish Ethical Review Authority for the specific linkage, Statistics Sweden and The National Board of Health and Welfare will both independently review the request to ensure it complies with the law regulating confidentiality in this instance (Chapter 24, 8§, The Swedish Publicity and Confidentiality Act 2009:400). If permission is given, the linkage is technically uncomplicated as all the registers are based on the unique personal identity number that all residents of Sweden have. Linked

data are released anonymised with a serial number replacing the personal identity number.

LymphomaBase

LymphomaBase is an existing linkage of the Swedish Lymphoma Register, all national health registers and the Total Population Register. The latest edition includes events until December 2019.

Statistical analyses

Disease control

For long-term follow-up, time to progression (TTP) was selected to measure disease control⁹⁰. Using the Kaplan-Meier estimator⁹¹ TTP was calculated from the date of diagnosis (date of tumour biopsy) to the date of progression of cHL. Patients were censored at time of death, in the absence of progressive disease or at time of last observation.

Morbidity

Cumulative incidence functions of second cancers, diseases of the circulatory system, and diseases of the respiratory system (and subgroups) were investigated with time of follow-up defined as beginning either on the date of diagnosis (II and III) or five years after the date of diagnosis (IV) until the first event, death or last observation. Death due to any cause was considered a competing event, as was progressive cHL in analysis of second cancers.

Hazard ratios (HR), with 95% confidence intervals (95%CI), were calculated using a Cox regression model censoring for the same events used as competing events in the investigation of cumulative incidence functions.

Survival

Overall survival was measured, with the Kaplan-Meier estimator, from the date of diagnosis until the date of death, censoring at the date of last follow-up or at the date of emigration.

Relative survival rates (RSR) were calculated using the Ederer II method⁹² for all patients and selected subgroups. For the early progression subgroup, early progression was measured as a time-varying exposure by which all patients were considered as being without early progression at diagnosis and early progression started at the date of progression. To assess expected survival, life charts, for Sweden and Norway, stratified for age, sex, and calendar period, were used.

Years of life lost was calculated as the remaining expected survival for a matched individual (age, sex, and calendar period) at the date of death, using the average life expectancy table for 2020⁹³. The resulting years of life lost

from each event were then grouped according to cause of death such as second cancers, cardiovascular disease, and other. Among patients, years of life lost to cHL were also calculated.

Ethical considerations

Studies in this thesis were entirely based on linking governmental health registers. As all the registers used (except for the Swedish Lymphoma Register) are mandatory, individual patients may not opt out of adding their data. Thus, approval from the Ethical Review Authority to perform a linkage without consent from each person included in a study removes any opportunity to give or withhold consent. Data released is anonymised, but the cohorts are relatively small and there are few events. This constitutes a risk of compromising the personal integrity of patients, and to a lesser degree comparators, included in the studied cohorts. Some of this risk and impact can be mitigated by not publishing results that are too granular, for example by grouping events that number less than three individuals and by minimising the number of researchers who handle raw data.

Another potential ethical problem is the methodology of years of life lost. This measures the potential number of years of life lost and provides information on an important aspect of the impact of exposure on long-term survival. But the method might also inadvertently suggest that the life of an elderly person is assigned less value.

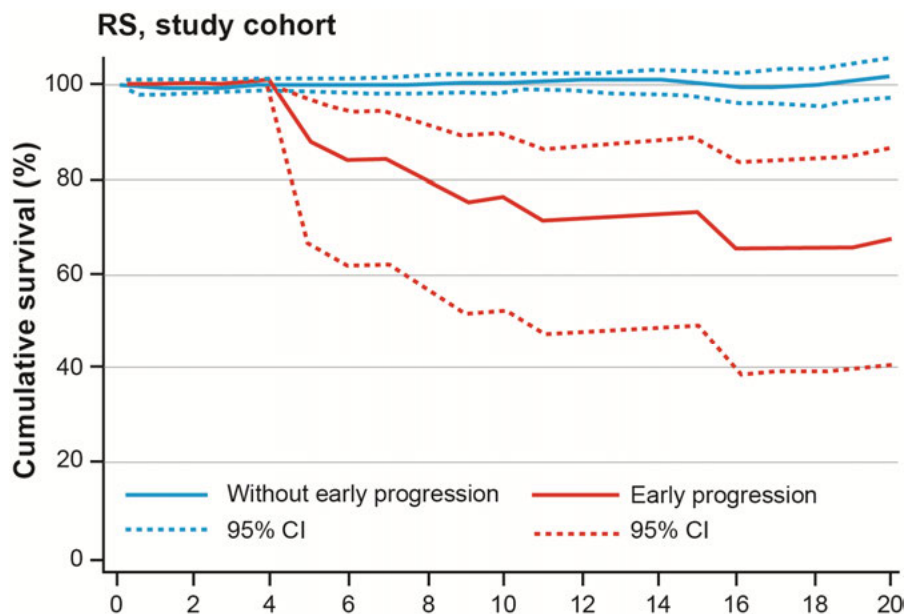
Results

Main findings

- Long-term survival among patients with early-stage cHL treated with combined modality is excellent with marginal to no excess mortality. The only analysed subgroup with significant excess mortality comprises patients with progressive disease within five years (I and III).
- With long-term follow-up, second cancer is the leading cause of death among patients with no similar effect from cardiovascular disease (III and IV).
- Excess malignancies exist among patients, HR 1.6 (95%CI, 1.1–2.4), but on a lower level than those reported in earlier published cohorts (II, III and IV).
- The incidence of diseases of the circulatory system among patients is increased, HR 1.4 (95%CI, 1.1–1.8), but to a lesser extent than in earlier publications, and with no visible trend towards an increasing risk with longer follow-up (II, III and IV).
- Hazard ratios for diseases of the respiratory system are significantly elevated, 2.6 (95%CI, 1.6–4.3) and 1.8 (95%CI, 1.4–2.4) in the earlier and later cohort respectively. In the earlier cohort this excess is almost exclusively consisting of the diagnosis of asthma, whereas the later cohort reports no effect from diagnosis of asthma (II, III and IV).

Paper I

During 1999–2005, a total of 364 patients with early-stage cHL, entered in the Nordic register, were treated with ABVD x2 or x4 and 30 Gy limited field radiotherapy in Sweden and Norway. Median age on diagnosis was 33 years (range 18–77). The cumulative proportion of patients without progression was 93% at five years of follow-up with only one progression occurring later than five years from diagnosis. Overall survival was 98% and 96% at the five-year and ten-year follow-up, respectively.



Years since diagnosis

	Years since diagnosis	N. at risk	Relative survival	95% Ci
Without early progression	0	364	–	–
	5	333	1.00	0.98–1.01
	10	327	1.01	1.98–1.03
	15	226	1.01	1.97–1.03
Early progression	0	0	–	–
	5	20	0.88	0.65–0.97
	10	17	0.76	0.52–0.90
	15	10	0.73	0.49–0.88

Figure 6. Comparing relative survival of patients with early progression (<5 years from diagnosis) with patients without early progression, after treatment with ABVD x2 or ABVD x4 followed by 30 Gray radiotherapy limited field, 1999-2005 in Sweden and Norway. Showing cumulative survival, with 95% confidence interval (CI), as a percentage of expected survival according to population life tables from Sweden and Norway. Number at risk shown in the table below.

Abbreviations: RS: relative survival. ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine.

Relative survival for the cohort is equal to that of the general population during follow-up (median 16 years for survival). In analysed subgroups (mediastinal involvement, bulky mediastinal involvement, mediastinal and axillary involvement, two cycles of ABVD, four cycles of ABVD, age below 40 years at diagnosis, age above 39 years at diagnosis, early progression of cHL, and

no early progression of cHL) only patients with early progression showed statistically significant excess mortality than in the general population (Figure 6).

Paper II

The 215 Swedish patients (Table 4) from the cohort studied in Paper I, and 860 matched comparators (recruited from the Total Population Register) were linked to national health registers. Median follow-up for the linked population was 16 years (range 12–19).

Table 4. Characteristics of patients with early-stage classical Hodgkin lymphoma treated with two or four cycles of ABVD followed by 30 Gy limited field radiotherapy 1999-2005 in Sweden, n=215 (female, n=107).

Patient and Disease Characteristics	Treatment		
	Two Cycles of ABVD	Four Cycles of ABVD	Mediastinal Radiotherapy ^a
<i>Age at diagnosis, years, median 34 years (range, 19–77 years)</i>			
18–39, n = 127	38	89	95
40–59, n = 57	31	26	25
≥ 60, n = 31	24	7	10
<i>Extent of disease</i>			
Bulky ^b	0	46 ^c	37
Mediastinum	30	100	130
Mediastinum and axilla	5	24	29

Abbreviation: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

^aLimited-field radiotherapy, guidelines for target fields available in the Data Supplement.

^b≥ 0.33 of internal thoracic diameter at Th5–6 level on a posterior anterior chest x-ray or mass/conglomerate > 10 cm in largest diameter on computed tomography.

^cOf these, 21 patients had mediastinal bulk.

Of the 215 patients 30 were diagnosed with at least one second cancer (any malignancy, except for non-melanoma skin cancer) corresponding to HR 1.5 (95%CI, 1.0–2.4). Individual malignancies were not analysed due to lack of power.

Excess diseases of the circulatory system was statistically significant, with 60 patients receiving at least one diagnosis during follow-up, resulting in HR 1.5 (95%CI, 1.1–2.0). Of analysed individual cardiovascular diagnoses (hypertension, coronary heart disease, heart failure, ischemic cerebrovascular disease, and venous thromboembolism) only venous thromboembolism was statistically significantly increased, HR 3.9 (95%CI, 1.9–7.2). If excluding the

first six months of follow-up and censoring at time of progressive cHL or second cancer, the significance in the risk of venous thromboembolism diminished, HR 2.2 (95%CI, 0.9–5.5).

Significantly more patients were diagnosed with at least one respiratory disease, HR 2.6 (95%CI, 1.6–4.3). This effect was almost exclusively caused by an excess risk of diagnosis of asthma, HR 3.5 (95%CI, 1.8–6.8).

The proportions of individuals with coexisting diagnoses from two or three of the investigated groups (second cancer, diseases of the circulatory system and diseases of the respiratory system) did not differ significantly between patients and comparators (Figure 7).

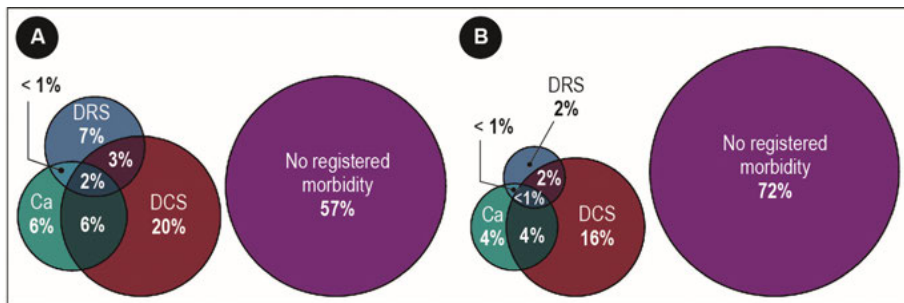


Figure 7. A) Patients treated, with ABVD $\times 2$ or $\times 4$ followed by 30 Gray limited field radiotherapy, for classical Hodgkin lymphoma stage IA-IIA in Sweden during 1999-2005, showing proportions of patients with any second Ca, DCS, DRS, and proportions of patients with combinations of morbidities. B) Proportions of comparators with any Ca, DCS, DRS, and combinations of morbidities.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine. Ca: cancer. DCS: diseases of the circulatory system. DRS: diseases of the respiratory system.

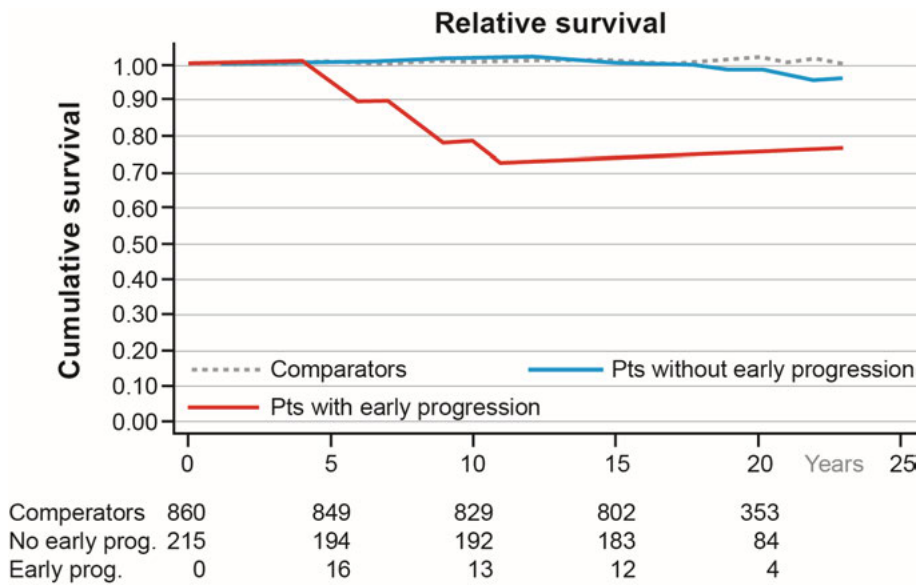
Paper III

The terms for the linkage used in Paper II permitted a repeat linkage with the same parameters after three years resulting in a median follow-up of 19 years for morbidity and 20 years for mortality.

Excess morbidity in second cancer, as well as diseases of the circulatory system, and respiratory systems were roughly unchanged, HR 1.6 (95%CI, 1.1–2.4), 1.4 (95%CI, 1.1–1.8) and 2.3 (95%CI, 1.4–3.7) respectively.

Updated analysis of survival resulted in relative survival for patients, without early progression, where the 95%CI still span the expected survival of the general population. There is, however, a visible trend towards possible excess mortality in the last part of follow-up (Figure 8). In analyses of years of life lost according to cause of death, 1.17 years/patient and 0.41 years/comparator were lost to second cancer ($p=0.004$) whereas 0.29 years/patient and 0.49 years/comparator were lost to diseases of the circulatory system ($p=0.38$).

Other causes resulted in a loss of 0.70 years/patient and 0.59 years/comparator ($p=0.68$). In addition, 0.50 years/patient were lost to progressive cHL. Among patients 15 deaths were caused by second cancer, 5 in the gastrointestinal tract (three with distal localization), 3 in the lymphoid and haematopoietic system, and 2 in the respiratory system. No deaths were caused by breast cancer. Causes of death were known for all 34 patients but unknown for 8 out of 93 comparators.



Abbreviation: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine.

Figure 8. Comparing relative survival of patients with early progression (<5 years from diagnosis) with patients without early progression, treated two or four cycles of ABVD followed by 30 Gray radiotherapy limited field, 1999-2005 in Sweden. Showing cumulative survival, with 95% confidence interval (CI), as a percentage of expected survival according to population life tables. Number at risk below.

Paper IV

Identified in the existing linkage LymphomaBase, 524 patients (and 5242 comparators), aged 18–65 years, diagnosed with early-stage cHL, between 2006 and 2015 were treated with combined modality. Median age on diagnosis was 35 years (interquartile range, IQR, 26–48) with a median follow-up of 8 years (range 5–15).

There was no excess risk of second cancer, HR 1.1 (95%CI, 0.6–1.8) during follow-up (starting five years after diagnosis). Risk of diseases of the circulatory system was elevated, HR 1.3 (95%CI, 1.0–1.8). In analyses of subgroups,

the risk of heart failure, HR 2.6 (95%CI, 1.3–5.0) was significantly elevated. Whereas the HR for diseases of the respiratory system was increased, 1.8 (95%CI, 1.4–2.4), risk was not increased in any of the analysed subgroups.

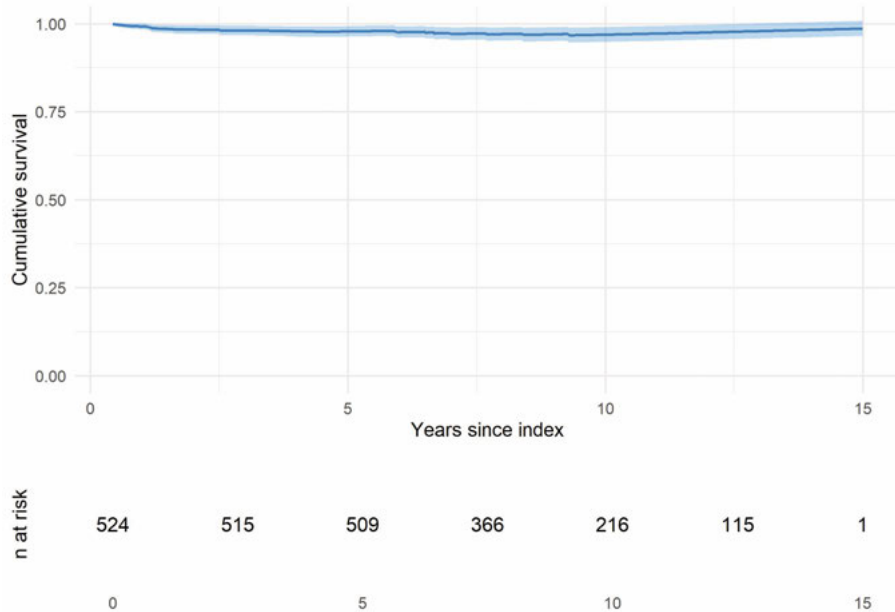


Figure 9. Relative survival of patients diagnosed with stage I or IIA classical Hodgkin lymphoma, 2006–2015 in Sweden, treated with two or four cycles of ABVD followed by 20 or 30 Gray limited field or involved site/involved node. Showing cumulative survival, with 95% confidence interval (CI), as a percentage of expected survival according to population life tables. Number at risk below.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine.

During follow-up 24 patients died, resulting in a relative survival rate of 0.98 (95%CI, 0.96–0.99) and 0.97 (95%CI, 0.95–0.99) at 5 and 10 years of follow-up respectively (Figure 9). Thus, this cohort, in contrast with the preceding Nordic cohort (Paper I), has a small but statistically significant reduced relative survival rate. The cohort reported a loss of 0.10 years/patient and 0.14 years/comparator to second cancers ($p=0.85$). Cardiovascular disease caused the loss of 0.15 years/patient and 0.06 years/comparator ($p=0.02$) whereas 0.10 years/patient and 0.22 years/comparator were attributed to other causes ($p=0.15$). For the whole cohort, 0.60 years/patient were lost to progressive cHL. If analysed by time periods, patients diagnosed 2006–2010 lost 0.90 years/patient whereas those diagnosed 2011–2015 lost 0.36 years/patient.

Discussion and conclusions

The two cohorts studied in this thesis, treated with combined modality, display excellent long-term survival (Papers I, III and IV), and less excess morbidity compared with earlier published cohorts (Papers II, III and IV).

In patients with longer follow-up, an increased risk of second cancer exists, HR 1.6 (Papers II and III), but distinctly lower than in earlier published cohorts (SIR 4–5 and relative risk 4.6 respectively)^{50,71,72}. The absence of increased risk of second cancers in the cohort analysed in Paper IV may be the result of a too-short follow-up, but it is noteworthy that the increased risk in the cited cohorts was already clearly present five years after diagnosis.

The risk of diseases of the circulatory system, HR 1.4 (Papers II and III), and for the heart failure subgroup, HR 2.6 (Paper IV), is also reduced compared with results published earlier, reporting SIR 3.2 for coronary heart disease and SIR 6.8 for heart failure^{77,78}. An event in the National Cancer Register requires a tissue sample that demonstrates a new malignancy and is not dependent on being part of specialist care. In contrast, part of the respective excess morbidity reported in cardiovascular and respiratory diseases might be explained by an increased effect from surveillance. Patients probably are more likely than comparators to be diagnosed and receive treatment by a specialist clinic for a corresponding cardiovascular or respiratory condition, thereby skewing data from the National Patient Register. Thus, the relative level of morbidity among patients might thus be overestimated.

There is a distinct lack of published long-term follow-up of pulmonary toxicity. Whereas bleomycin is known to influence survival through acute pulmonary toxicity⁸², the elevated risk of diseases of the respiratory system, HR 1.8–2.3, did not seem to impact survival.

Despite clearly higher morbidity among patients than among comparators, survival did not seem to be impacted. There might be several explanations for this result. The method of relative survival (Ederer II) is known sometimes to overestimate survival during long-term follow-up. However, with comparator survival not deviating from the expected, when the method was used, such an error is unlikely in this instance. Smoking among cHL survivors is a risk factor that multiplied already elevated risks of morbidity, in particular of lung cancer^{50,78}. Smoking can be assumed to impact mortality as well, as lung cancer has been shown to be the largest contributor to excess mortality from second cancers in cHL survivors⁷⁵. The age adjusted prevalence of current smokers

was 13% in 2019 and has been reduced by >45% in Sweden⁹⁴ since 1990. This may have impacted morbidity and mortality in these cohorts compared with earlier reports. It may also impact whether these results can be reproduced in countries with higher proportions of current smokers. Lower mortality from cardiovascular disease in the general population in Sweden (and in many other countries), in recent decades⁹⁵ may also be evident among cHL survivors. Another problem with reproducibility is the strong influence of national or local tradition on how radiotherapy is implemented. For example, published radiotherapy fields from the HD17 trial, defined as involved node, are clearly much more extensive, than involved node as it is implemented in Sweden, with relatively high radiation doses given to organs at risk⁹⁶.

The visible trend towards excess mortality at the end of follow-up (Paper III) instigated a study of causes of death; the trend, however, should be interpreted cautiously. The finding is not statistically significant as it is found at the very end of follow-up with a reduced number of patients at risk. Early during follow-up, progressive cHL is the dominant cause of death, resulting in measurable excess mortality (Paper IV). This is in line with analyses of pooled results of the randomised trials of the GHSG, where progression-free survival is shown to be highly correlated to overall survival⁹⁷. There is, however, an intriguing tentative finding in the later cohort (Paper IV), i.e., the impact on years of life lost seems to be reduced in patients diagnosed more recently. This might be due to a more precise definition of the extent of cHL using FDG-PET/CT, which reduces the risk of errors in defining stage and target when radiotherapy is used. There might also be an effect from the introduction of brentuximab vedotin and immune checkpoint inhibitors in treatment, with improved survival in relapsed or refractory cHL^{57,98}. With longer follow-up, second cancer becomes the clearly leading cause of death according to years of life lost, with no detectable effect from cardiovascular disease (Paper III). In the later cohort, there is an early statistically significant excess of years of life lost to cardiovascular disease, but it is of questionable clinical significance (Paper IV).

In conclusion, the limited excess of cardiovascular disease and lack of impact on survival from cardiovascular disease, in cohorts with only rudimentary screening, might argue against allocating resources to screening in this area. Whereas certain excess second cancer is noted, and this is the leading cause of death on long-term follow-up, no statistically significant impact on relative survival is evident to date. The only cause of death that can be correlated, in time to statistically significant excess mortality, in these cohorts is progressive cHL. This argues for combined modality treatment, which thus far has resulted in superior levels of disease control in early-stage cHL.

Future perspective

Longer follow-up is required to map second cancer among patients in the second cohort (Paper IV). There is also a need to investigate the risk of second cancer among patients who received radiotherapy using volumetric modulated arc therapy (VMAT). This method was not yet used in a relevant proportion in the cohorts studied in this thesis. It generally results in lower radiation doses to healthy tissue but also involves larger volumes of healthy tissue.

With brentuximab vedotin and immune check point inhibitors included in first-line treatment of advanced stage cHL, they can be expected to eventually make it into first-line treatment of early-stage disease. This can be achieved in three ways. First, if they are assessed as resulting in less toxicity than the current standard of therapy for early-stage disease (i.e., combined modality), the new treatment strategies for advanced stage disease can be applied without change, or perhaps merely by adapting the number of cycles, to early-stage disease. A second alternative is to add the new agents to the current standard of treatment, as in the phase II GHSG-trial NIVAHL, using N-AVD followed by 30 Gy involved site radiotherapy for intermediate stage cHL⁹⁹. This is not likely to reduce toxicity but seems to enhance disease control. The third method would be to replace chemotherapy and retain radiotherapy. This would be more attractive with immune checkpoint inhibitors as the combination with radiotherapy has potential synergies¹⁰⁰. Data is not available to accurately predict whether the strategy of reducing or excluding chemotherapy or of excluding radiotherapy, is the best means of achieving lower long-term toxicity. Regardless of which of these strategies is implemented, long-term follow-up will be required to monitor toxicity from the wider use of novel treatments.

Sammanfattning på svenska

Bakgrund

Klassiskt Hodgkinlymfom är en av de vanligaste tumörsjukdomarna bland unga vuxna. I mitten av 1900-talet var prognosen oftast dålig med kort förväntad överlevnad. Utveckling av strålbehandling och kombinationer av olika cytostatika har över tid förbättrat prognosen så att de flesta som drabbas nu kan botas. Det första genombrottet i utvecklingen var strålbehandling med stora fält och höga doser. Resultaten förbättrades sedan genom att ge cytostatikakombinationer inför strålbehandlingen.

Parallellt med denna utveckling uppmärksammades en kraftigt ökad sjuklighet i form av andra tumörsjukdomar, hjärt-kärlsjukdomar och lungsjukdomar bland botade patienter. Den ökade sjukligheten, s.k. seneffekter, resulterade i att överlevnaden för botade patienter var betydligt sämre jämfört med den övriga befolkningen. Seneffekterna från behandlingen kunde till stor del kopplas till den omfattande strålbehandlingen. Detta blev drivkraften till att stegvis minska strålfält och stråldoser. Målsättningen var att inte samtidigt försämra chansen att lyckas uppnå bot.

Vid klassiskt Hodgkinlymfom med omfattande spridning i kroppen innebar utvecklingen av effektivare kombinationer av cytostatika att strålbehandling helt kunde uteslutas. Vid begränsad utbredning av lymfomet, så kallade tidiga stadier, har kombinationsbehandling som består av kortvarig behandling med cytostatika följt av strålbehandling en större chans att bota. Under det senaste årtiondet har en internationell trend varit att avstå strålbehandling även vid tidiga stadier. Tanken har varit att den försämrade chansen till bot kompenseras genom en minskad risk för seneffekter. I de flesta fall har dock chansen till bot försämrats så mycket att studierna inte uppnått sina mål eller avbrutits i förväg. Tanken om att den försämrade chansen till bot kan vägas upp av färre seneffekter från strålbehandlingen innehåller dessutom ytterligare en svaghet. Den förmodade omfattningen av seneffekter baseras på forskningsresultat avseende strålbehandling som inte längre är i bruk.

Målsättning och metoder

Målsättningen med denna avhandling är att fastställa nivåer av sjuklighet och överlevnad för patienter som behandlats för tidiga stadier av klassiskt Hodgkinlymfom med kombinationsbehandling där strålfält och dos tydligt

minskats. Nivåer av sjuklighet och överlevnad hos patienterna jämförs med den övriga befolkningen och med rapporterade nivåer hos tidigare behandlade patienter. Grupper av patienter som fått sådan behandling har identifierats i lymfomregister och samkörts med nationella hälsoregister. Grupperna har analyserats i fyra delarbeten.

Delarbete I

Under 1999–2005 hade vi i Sverige och Norge gemensamma riktlinjer för behandling av tidiga stadier av klassiskt Hodgkinlymfom. Där ingick en standardbehandling med cytostatika som fortfarande gäller. Strålfälten minskades i en omfattning som vid denna tidpunkt sannolikt var unik som standardbehandling. Ett gemensamt register, det så kallade Nordiska registret, infördes för kvalitetskontroll.

Efter en uppföljning på median 16 år uppvisade de 364 identifierade patienterna från registret en överlevnad som statistiskt inte skilde sig från den övriga befolkningen. I analyser av olika undergrupper av patienter (bland annat avseende lymfomutbredning, ålder och kända risker för återfall) så var det endast de patienter som fick återfall av lymfom som hade en statistiskt säkerställd försämrad överlevnad.

Delarbete II

De 215 svenska patienterna som identifierades i delarbete I samkördes mot nationella hälsoregister för att fastställa nivåer av nya tumörsjukdomar, hjärt-kärlsjukdomar samt lungsjukdomar. Analyser visade en ökad frekvens för alla tre kategorier jämfört med övriga befolkningen (ca 50% ökning för tumörer och hjärt-kärlsjukdom samt ca 160% ökning för lungsjukdom), men en betydande minskning jämfört med tidigare behandlade patienter.

Delarbete III

En förnyad samkörning avseende patienterna i delarbete II genomfördes. Efter en medianuppföljning på 20 år var nivåerna avseende sjuklighet ungefär oförändrade förutom sjunkande förekomst av lungsjukdomar. I slutet av perioden för uppföljning kunde en tendens till överdödlighet anas, dock inte statistiskt säkerställd. Vid undersökning avseende dödsorsaker, med beräkning av förlorade levnadsår, visade sig död på grund av annan typ av tumörsjukdom vara statistiskt överrepresenterad. Däremot var död på grund av hjärt-kärlsjukdom inte ökad jämfört med övriga befolkningen.

Delarbete IV

I en sedan tidigare utförd och sparad stor samkörning av hela svenska lymfomregistret med nationella hälsoregister identifierades 524 patienter som fick diagnosen tidigt stadium av klassiskt Hodgkinlymfom 2006–2015 och behandlades med en kombination av cytostatika och strålbehandling. Med en medianuppföljning på 8 år sågs ingen ökning av tumörsjukdomar, en mer blygsam ökning av hjärt-kärlsjukdomar (30% ökning) och en tydlig ökning av lungsjukdomar (80% ökning). Överlevnaden var mycket god men det fanns en statistiskt säkerställd men marginell minskning. Patientgruppen hade 98% av förväntad överlevnad. Under denna period var klassiskt Hodgkinlymfom den helt dominerande dödsorsaken vid analys av förlorade levnadsår.

Slutsatser

Analysen visar att behandlingsorsakad tumörsjukdom, hjärt-kärlsjukdom och lungsjukdom förekommer även efter cytostatikabehandling kombinerad med mer modern strålbehandling. Nivån är dock på en mycket lägre nivå än vad som rapporterats tidigare. Överlevnaden bland patienter är mycket god och avviker endast marginellt, eller inte alls, från förväntad överlevnad. Under den period som överlevnaden avviker från det förväntade är klassiskt Hodgkinlymfom den helt dominerande dödsorsaken. Dessa resultat talar för att behålla rekommendationen att behandla tidiga stadier med en kombination av cytostatika och strålbehandling så länge detta innebär en förbättrad chans till bot.

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