Long-term efficacy and late complications after chemo- and radiotherapy in aggressive non-Hodgkin's lymphoma

Moser, E.C.

Long-term efficacy and late complications after chemo- and radiotherapy in aggressive non-Hodgkin's lymphoma

E.C. Moser, 2006

Long-term efficacy and late complications after chemo- and radiotherapy in aggressive non-Hodgkin's lymphoma

ISBN:
Drukbemiddeling: GoPublic V.O.F.
Layout: A.J. van Houwelingen (www.gopublic.nl)
Cover: *"So why so sad"* door Sunny de Vroedt, 2002
onder bemiddeling van www.kunstwerkkopen.nl

KUNSTWERKKOPEN.NL

Financial support for printing of this thesis by SKOL (Stichting Klinische Oncologie Leiden), the EORTC (European Organisation of Research and Treatment of Cancer), J.E. Jurriaanse Stichting and Roche NL B.V is gratefully acknowledged.

Long-term efficacy and late complications after chemo- and radiotherapy in aggressive non-Hodgkin's lymphoma

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr.D.D.Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor Promoties
te verdedigen op 21 februari 2007
klokke 16.15 uur
door
Elizabeth Charlotte Moser
geboren te Amsterdam op 26 maart 1973

Promotiecommissie:

Promotores: Prof. Dr. E.M. Noordijk
Prof. Dr. J.C. Kluin-Nelemans
(Universitair Medisch Centrum Groningen)

Referent: Prof. Dr.R.Willemze

Leden: Prof. Dr. F.E.van Leeuwen
(Nederlands Kanker Instituut Amsterdam)
Dr. J.M.M. Raemaekers
(Universitair Medisch Centrum Nijmegen)
Dr. S. le Cessie

The work presented in this thesis was (financially) supported by the Dutch Cancer Society (Koningin Wilhelmina Fonds) and done on behalf of the EORTC Lymphoma Group.

Voor mijn vader en Roos,
die door wie ze waren en wat zij hebben gegeven,
voor altijd in mij verder leven.

Contents

Chapter 1

Introduction

Introduction

In this thesis, the long-term follow-up of patients with aggressive non-Hodgkin's lymphoma (NHL) treated in 4 subsequent European Organisation for Research and Treatment of Cancer (EORTC) trials is described, focusing both on efficacy and late complications. The introduction will start with an overview of the biology, classification, treatment and response estimation of aggressive NHL. Next, the EORTC Lymphoma Group trials are presented. Finally, the background and statistical considerations in analysis of long-term efficacy and late effects of NHL treatment are discussed.

Non-Hodgkin's Lymphoma

The term non-Hodgkin's Lymphoma denotes a group of more than 30 lymphoproliferative malignancies that lack the pathologic characteristics of Hodgkin's Lymphoma (HL). The common link for this diverse group of neoplasms is the monoclonal expansion of malignant B- or T-cells. Acute lymphoblastic leukaemia, chronic lymphocytic leukemia, and HL are also malignancies of the immune system that occasionally display clinical and pathologic features that overlap with nodal or extranodal NHL. [1, 2] NHL can appear at any age, although rarely during the first year of life. Like HL, NHL usually originates in lymphoid tissues and can spread to other organs. However, unlike HL, multiple sites are frequently involved, and extranodal lesions are common, sometimes being the only site of disease. Progression of disease is less orderly than in HL, and prognosis strongly depends on the histological type of NHL. Although the different lymphomas vary widely in natural history and response to therapy, they can be categorized into two groups: *indolent* (low grade) lymphomas and *aggressive* (intermediate- and high-grade) lymphomas. This categorization is useful and relevant for the selection of treatment, including chemo-, immuno- and radiotherapy.[2]

Classification of NHL

Considering the diversity of NHL, it is crucial to obtain clear and detailed pathologic information in every patient. Information must be carefully interpreted, recognizing the complexity and limitations of present classification systems. [1] Over the past 40 years, the histological classification of NHL has changed. In the United States, the Rappaport classification was widely used, whereas in Europe the Kiel classification was often applied. [3] Communication and comparison of clinical trials were therefore extremely difficult. In 1982, international collaborative efforts led to the Working Formulation for Clinical Usage (WF, Table 1) that 'translated' the different classifications and grouped the different subtypes into clinically relevant grades, e.g. low, intermediate and high grade lymphomas. [4]

Table 1. Histological classification of NHL by the Working Formulation [4]

Working Formulation (1982)
Low-grade
A. Small lymphocytic
B. Follicular small cleaved
C. Follicular mixed, small cleaved, and large cell
Intermediate-grade
D. Follicular large cell
E. Diffuse mixed small and large cell
F. Diffuse small cleaved cell differentiated lymphocytic
G. Diffuse large cell
High-grade
H. Large cell cell immunoblastic
I. Lymphoblastic
J. Small noncleaved: Burkitt's, non-Burkitt's

Over the past 15 years, new information (immuno-histopathological and molecular-genetic) has become available, leading to recognition of new entities and modification of existing lymphoma categories. The International Lymphoma Study Group published a proposal for a Revised European-American Classification of Lymphoid Neoplasms (REAL). [5, 6] It has since been adapted with slight modification and is now termed the World Health Organization (WHO) classification. [2] The categorization maintains the prognostic groups, which correspond with the overall selection of treatment (Table 2). However the pathological expression *grade* used by the WF has changed into a clinical pattern term *indolent or aggressive* for the WHO. [2, 4] The distinction between B and T cell neoplasms is introduced, leukaemia's and new categories are added. While many Natural Killer (NK) and T-lymphomas are included in the indolent group, the relatively uncommon T-cell lymphomas (such as for example peripheral T-cell lymphoma and anaplastic large cell lymphoma) are categorized in the aggressive histology group (Table 2).

This thesis is based on 4 EORTC trials, designed for intermediate or high grade NHL according to the WF. In all trials histological classification was performed by the local pathologist and reviewed by a Lymphoma Pathology Panel after randomisation. As several of these trials were designed even prior to the WF classification NHL categories have been redefined as intermediate- and high-grade histology following the WF. [4] WHO subgroups as anaplastic large cell lymphoma and mantle cell lymphoma were not yet distinguished and distinction between T/NK- and B-cell neoplasms was not used. Therefore, one has to realize that these entities were included in our analyses (Table 3).

Table 2. Histological classification by the World Health Organization [2]

World Health Organization (2001)
Indolent
B-cell neoplasms*:*
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukaemia, Lymphoplasmacytic lymphoma (Waldenström), Plasma cell myeloma, Hairy cell leukaemia, Follicular lymphoma (grade 1+2), or Marginal zone B-cell lymphoma
T-cell neoplasms:
T-cell large granular lymphocyte leukaemia, Mycosis fungoides, T-cell prolymphocytic leukaemia
Natural killer cell neoplasms:
Natural killer cell large granular lymphocyte leukaemia
Aggressive
B-cell neoplasms:
Follicular lymphoma (grade 3), Diffuse large B cell, Mediastinal and Mantle cell lymphoma
T-cell neoplasms:
Peripheral T-cell lymphoma, Anaplastic large cell lymphoma, T/null cell lymphoma and other rare T-cell lymphomas
Highly Aggressive
B-cell neoplasms:
precursor B-Lymphoblastic leukaemia/ lymphoma, Burkitt's lymphoma
T-cell neoplasms:
precursor T-Lymphoblastic leukaemia/ lymphoma, Adult T-Lymphoblastic leukaemia/lymphoma

Table 3. Histological characteristics across 4 EORTC-studies, according to the Working Formulation after revision by the EORTC Lymphoma Pathology Panel.

Histology	**20802**	**20855**	**20901**	**20932**	**Total**
Low-grade					
A-C. Small lymphocytic, follicular small cleaved or follicular mixed, small cleaved, and large cell	31	16	5	0	52 (5%)
Intermediate-grade					
D. Follicular large cell	5	23	11	0	39 (4%)
E. Diffuse mixed small and large cell	23	52	20	3	98 (10%)
F. Diffuse small cleaved cell differentiated lymphocytic	22	45	17	1	85 (9%)
G. Diffuse large cell	57	181	165	5	408 (43%)
High-grade					
H.Large cell cell immunoblastic	15	45	4	3	67 (7%)
I. Lymphoblastic	14	7	1	0	22 (2%)
J. Small noncleaved: Burkitt's, non-Burkitt's	6	7	2	0	15 (2%)
Unclassified	16	37	86	25	164 (17%)
Total	**189**	**413**	**311**	**39**	**952**

Aggressive lymphoma

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL (30% of all NHL and 80% of all aggressive NHL) and its incidence has been increasing over the last decades. The median age of patients is in the 7th decade, but ranges broadly and also includes children. The male/female ratio is almost equal. DLBCL is heterogeneous by morphologic, immunophenotypic and molecular cytogenetic criteria. The characteristic cell of diffuse large cell lymphoma is large (nuclei at least twice the size of a small lymphocyte), with vesicular nuclei, prominent nucleoli and basophilic cytoplasm. The immunophenotype is characterized by pan B-cell markers (CD19, CD20, and CD22) and clonal surface immunoglobulin (usually IgM) in about 75% of the patients and CD10 in about 25% of patients. Patients with DLBCL typically present with a growing mass at a single nodal or extranodal site. Forty percent are, at least initially, confined to extranodal sites. Although DLBCL is an aggressive disease that will be, without treatment, lethal (median survival of 8 months), it is potentially curable in all stages. Almost half of the patients present with localized disease and approximately 80-90% of this category of patients can be cured with combined modality treatment. Patients with advanced stages (II or more, see Table 4) have a worse prognosis. [1, 2]

Recent gene expression profiling studies have identified the following distinct subgroups of DLBCL: germinal center B-cell–like (GCB), activated B-cell–like (ABC), and primary mediastinal DLBCL. [7] The GCB subgroup is characterized by it's molecular signature and sometimes the translocation t(14;18)(q32;q21). GCB has a better prognosis than the ABC subgroup. [8] The molecular signature of the ABC subgroup is distinctly different and is characterized by overexpression of a group of genes that are upregulated in peripheral-blood B cells when these are activated by mitogenic stimulation *in vitro*. The primary mediastinal subgroup can be distinguished from the other subgroups by its unique gene expression profile more closely related to Hodgkin's lymphoma. However, patient survival is similar to that of GCB DLBCL. [9]

Mantle cell lymphoma

Mantle cell lymphoma is one of the 'new' NHL entities, not listed in the WF. Many cases were termed as *diffuse small cleaved cell lymphoma* in the WF. Of advanced stage NHL patients approximately 10% are nowadays classified as mantle cell lymphoma. This NHL is found only in adults, and a median age of 60 years and high male/female ratio of at least 2:1 is reported. [10-12] The tumour is exclusively composed of small to medium-sized lymphoid cells, slightly larger than normal lymphocytes, with more dispersed chromatin, pale cytoplasm and inconspicuous nucleoli. Immunophenotyping shows B cell markers in combination with CD5+, CD23-, surface IgM+ and IgD+. In the majority of cases a translocation t(11;14)(q13;q32) is observed, resulting in cyclin D1 overexpression, which is an important hallmark of the disease. The disease is usually widespread at diagnosis and is significantly more aggressive than other small lymphocytic lymphomas. [10-13]

Peripheral T-cell lymphoma

Lymphoma of the mature (post-thymic) T-cells is termed peripheral T-cell lymphomas,

since these express only CD4 *or* CD8, unlike thymocytes, which express CD4 *and* CD8. The WF did not identify T-cell lymphomas as separate entities. Recognition is important as these lymphomas have an aggressive natural history and are considered as having a far worse prognosis than most B-cell aggressive lymphomas. [14, 15] Several different entities are being recognized, all rare, frequently extranodal and invariably associated with a poor outcome. Diagnosis by morphology alone is difficult and requires an experienced hemato-pathologist.

Anaplastic large cell lymphoma (ALCL)
Anaplastic large cell lymphoma is a T-cell lymphoma, defined by its expression of CD30 and EMA+, and accounts for about 3% of the adult NHL. Cases have been reported in all age groups; however 15-30% of the patients are younger than 20. [16] Two entities are recognized: one with a t(2;5) resulting in ALK over expression. This ALK+ ALCL has an excellent prognosis. ALCL's without the t(2;5) are considered another disease, and do far worse. [16-19]

Burkitt's lymphoma
Burkitt's lymphoma is a highly aggressive diffuse lymphoma composed of uniform mature B-cells of follicular centre origin. The cells are medium-sized with round nuclei and multiple nucleoli and relatively abundant basophilic cytoplasm, which give the cells a cohesive appearance. The proliferation rate but also spontaneous cell-death rate is extremely high. The immunophenotype is characterized by CD10, abundant clonal surface immunoglobulin, usually IgM, and the pan-B lineage markers (CD19, CD20, and CD22). EBV genes can be demonstrated in the tumour cells in most African patients and in 25-40% of the cases associated with AIDS. The translocation t(8;14) is found in 90% of Burkitt's lymphoma. Less frequently are the t(2;8) or t(8;22) translocations observed. All cases harbour translocations involving the *MYC* gene. [20-22]

Staging and prognostic factors
Although histology is the predominant determinant of prognosis in NHL, staging remains important for selection of treatment strategies and predicting prognosis in each histological category. The Ann Arbor staging classification system (Table 4), developed for HL, is also used for NHL. [23] This system reflects the number of sites of involvement and their relation to the diaphragm and existence of B-symptoms and extranodal disease. The Ann Arbor staging system is considered more relevant for HL than for NHL and in addition other prognostic factors have been identified in patients with NHL. [24] Mauch *et al* identified prognostic factors in patients with stage I and II aggressive NHL, such as bulky disease and the number of extranodal sites involved, which are of particular interest in relation to radiotherapy. [25]

Table 4. Ann Arbor Staging Classification of NHL*

Stage I	Involvement of a single lymph node region (I) or single extra lymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or with localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) or with localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of more than one extralymphatic organ or site with or without associated lymph node involvement
Stage is accompanied by an **A** as asymptomatic; or **B** as with fever, and/or night sweats, and/or weight loss of more than 10% of body weight.	

*In the AJCC Cancer Staging Manual 5Th edition (1997), published by Lippincott-Raven Publishers, Philadelphia, USA

An international team developed the International Prognostic Index (IPI), also known as the *Shipp criteria*, consisting of five risk factors that could significantly predict overall survival in aggressive NHL (Table 5). The sum of the five adverse risk factors creates 4 categories: low, low-intermediate, high-intermediate and high risk. In new NHL patients, the IPI has become an important prognostic tool and is besides histology and staging used in treatment selection (Table 5, 6).

Table 5. International Prognostic Index (IPI) for aggressive NHL*

Adverse risk factors:		
Age 60+		
Serum LDH above normal		
Performance score of 2 or more		
Ann Arbor stage III or IV		
More than one extranodal site involved		
	IPI score	**5 years overall survival (%)**
Low-risk	0-1	73
Low-intermediate	2	51
High-intermediate	3	43
High-risk	4-5	26

*The International Non-Hodgkin's Lymphoma Prognostic Factors Project.

A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-94

The predicted 5-years survival rates for the 4 IPI categories were (estimated in patients treated with CHOP-like chemotherapy, without rituximab) 73%, 51%, 43% and 26%, respectively. [26]

As the IPI was introduced in the nineties, this tool was not yet integrated in the 4 EORTC-trial protocols during 1980-1999. Nevertheless, all 5 risk factors were scored, and the IPI could be (retrospectively) estimated after the update in 2001.

Table 6. Survival by histologic aggressive NHL type and the International Prognostic Index (IPI).*

NHL diagnosis	*6- years overall survival*		*6-years failure-free survival*	
	IPI 0/1	**IPI 4/5**	**IPI 0/1**	**IPI 4/5**
Follicular	84%	17%	55%	6%
Mantle cell	57%	0%	27%	0%
Small lymfocytic	76%	38%	35%	13%
Diffuse large B-cell	73%	22%	63%	19%
Primary mediastinal large B-cell	77%	0%	69%	0%
High-grade B-cell, Burkitt-like	71%	0%	71%	0%
Peripheral T-cell	36%	15%	27%	10%
Anaplastic large T-cell/null cell	61%	83%	49%	83%

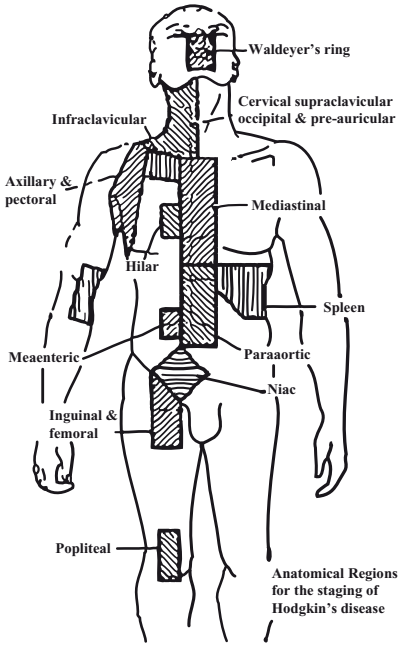
*Adapted from Armitage J.O., Lister T.A: Non-Hodgkin's lymphoma. In: American Society of Clinical Oncology Education Booklet, 1998; page 338

Most NHL patients are "clinically" staged (e.g. in contrast to pathological staging that consist of a staging laparotomy) based on physical examination, imaging and (bone marrow) biopsies. In the eighties, as computed tomography (CT) allowed evaluation of extranodal disease as well, the CT scan replaced the lymphangiogram in determining NHL involvement.[27] Accordingly, staging and response evaluation was routinely performed by CT scan in all 4 EORTC-trials (1980-1999). Bone marrow biopsy was mandatory and in case of doubt, especially if extranodal localisations showed residual involvement, supplementary biopsies had to be performed. Nowadays the MRI can help in case of doubt of extranodal disease (especially when localized in bone or the central nervous system). In the nineties Gallium-67 scanning was introduced for measuring response and detection of early recurrences. It appeared a prognostic indicator; a positive gallium scan at mid-course of chemotherapy leads only in 25% to a durable response, compared a 70% cure rate in patients whose gallium scan was normalized half-way chemotherapy treatment. [28] Recently, positron emission tomography (PET) scanning using 18F-fluorodeoxyglucose was shown to be a sensitive tool in detecting and response evaluation of aggressive NHL. It is quickly becoming an essential tool for making treatment decisions. [29] Both Gallium and PET scanning were not yet routinely used in the 4 EORTC-trials described in this thesis.

Treatment of aggressive NHL

Early stages

Until the 1980s, the majority of patients with early-stage aggressive NHL were treated with radiotherapy alone. With extended field radiotherapy (Table 7) up to 90% complete response rates were obtained with a dose of 40 Gy with 1.8-2 Gy per fraction, five times a week. [30, 31] However, relapses were frequently seen and less than half of the stage I patients were cured, whereas in stage II disease only 20% survived. Most of the relapses were extranodal or occurred outside the irradiated fields.[31] After more restrictive selection by staging laparotomy of stage I patients, extended fields of radiation yielded a 10-year relapse-free survival of 90-100%. But still, even staging laparotomy and total lymphoid irradiation yielded unsatisfactory



survival rates of 35-55% in stage II patients.[32] With the introduction of poly-chemotherapy, staging laparotomy became obsolete and radiation fields were reduced to the anatomic regions (Fig.1) defined by Kaplan and Rosenberg for staging of HL patients. This radiation of fields encompassing the anatomic regions of the initial involved sites is also noted 'involved-field'radiotherapy. [33-35]

Fig.1 Description of anatomic regions in Kaplan H.S, Rosenberg S.A: The treatment of Hodgkin's disease. Med Clin North Am 1966;50:1591

With the introduction of poly-chemotherapy, the debate started if treatment of early stage aggressive NHL needs combined treatment or chemotherapy alone. [36, 37] The addition of doxorubicin improved outcome even further and 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-like chemotherapy (Table 8) with additional involved field radiotherapy became the standard for many years. [38-43] This standard cures, depending on the initial IPI, 80-90% of patients with early stage aggressive NHL, and is based on the prospective randomized trial done by the South West Oncology Group (SWOG).[44] In this trial, eight cycles of CHOP was compared to the combination of three cycles followed by involved field radiotherapy (40 Gy with an optional boost of up to 55 Gy) in localized aggressive NHL, stage I or II non-bulky disease. [44] In retrospect were 70% of the patients graded as IPI-low risk. [45] At 5 years the overall survival was significantly better in the combined approach (72% vs. 82%, p=0.02). However, in a later update of the SWOG-data, the benefit of combined modality treatment diminished over time and Miller et al. suggested that patients with early stage modified high IPI yielded inferior survival and may require more than three cycles.[45] The Eastern Cooperative Oncology (ECOG) study 1484 also favoured adjuvant radiotherapy in early stage aggressive NHL. In this study, not 3 but 8 cycles of CHOP were given for early stage aggressive NHL. Additional radiotherapy (30 Gy in case of complete remission and 40 Gy in case of partial response) after 8 cycles of CHOP resulted in better disease control, although no significant overall survival benefit was found in the 15-year update. Cause-specific survival was not reported. [46]

The French Groupe d'Etude des Lymphomes de l'Adulte (GELA) compared the same 3 cycles of CHOP with involved field radiotherapy in early stage aggressive NHL to 3 courses of ACVBP (Table 8) with sequential consolidation chemotherapy in young patients with low-risk IPI. [47] Their results were very different, showing a better outcome in the chemotherapy alone-arm (5 years overall survival 80 vs. 88%). Although the CHOP-radiotherapy combination-arm was comparable to the SWOG-study, the chemotherapy alone arm was very different from CHOP due to the addition of several (high dose) cytostatic drugs. Longer follow-up of the GELA-cohort is needed to decide whether the standard 3 cycles of CHOP

with radiotherapy should be replaced by a more intensive chemotherapy regimen only.[48] Altogether, the number of cycles and the role of radiation therapy in early stage aggressive NHL are still under debate. We summarized the functional field definitions in Table 7, ranging from very small fields directed to initial or residual disease, as used today, to more extended fields used in the earlier days of less modern imaging and radiotherapy techniques. Currently, consolidation doses of 30 to 36 Gy are advocated for patients who attained an unquestionable complete remission following 3-6 cycles of chemotherapy (depending on initial IPI).[44-48] For initial bulky regions or uncertain CR higher doses are advised (40 Gy) and a persistent positive PET scan following chemotherapy is often believed to mandate a more aggressive approach.[47]

Advanced stages

The standard treatment for patients with advanced-stage aggressive NHL is combination chemotherapy, with CHOP as most commonly used regimen.[38] The EORTC CHOP-like standard became CHVmP/BV,[50, 51] consisting of cyclophosphamide, doxorubicin, and teniposide with prednisone, bleomycin and vincristine, whereas the GELA-standard in advanced aggressive NHL still is ACVBP (Table 8).[52] The GELA claims that this 'high dose CHOP-scheme' is superior to CHOP in poor-risk patients.[53]

As standard CHOP chemotherapy produces only 45-55% complete remissions and cures finally only one third of patients with advanced aggressive NHL, many alternatives for CHOP, containing more intensive, high-dose, sequential chemotherapy delivered within a relatively short timeframe,[49,54-59] or subsequent autologous bone marrow transplantation (ASCT)[60-63] are tried to improve outcome.

Table 7. Functional radiotherapeutic field definitions

Involved node radiotherapy	**Includes only the initially involved lymph nodes exclusively and encompasses their initial volume.** CT scans are mandatory and should be performed, whenever possible, in the treatment position with the use of image fusion capabilities. A pre-chemotherapy PET scan is strongly recommended to increase the detection of involved lymph nodes.
Involved field radiotherapy	**Includes not only the initially clinically enlarged lymph nodes but also the other lymph nodes within the same node region.** CT scans are mandatory (see Fig.1).
Extended field radiotherapy	**Includes the involved field as well as all the adjacent lymph node regions, divided in mantle or inverted Y fields.** In cases of supraclavicular lesions, the field would include the mantle field and the upper abdominal nodes and spleen. CT scans, but mainly lymphograms were used.
Mantle field radiotherapy	**Includes all (left and right) supradiaphragmatic lymph node regions: cervical, supraclavicular, axillary, infraclavicular, superior mediastinal, hilar and subcarinal nodes.** Mini-mantle fields exclude the mediastinum entirely.
Paraaortic/splenic field radiotherapy	**Includes paraaortic lymph nodes and spleen with a superior border matching the mantle field and a lower border at the aortic bifurcation (level L4).** Spleen hilar region (after splenectomy) or spleen irradiation is classically associated with the paraaortic field with minimized kidney irradiation.
Pelvic field radiotherapy	**Includes all (left and right) pelvic and inguinal lymph nodes**
Inverted Y field radiotherapy	**Combination of the paraaortic/spleen, pelvic and inguinal-femoral fields.**
Total nodal irradiation	**Combination of the mantle and inverted Y fields.**
Subtotal nodal irradiation	**Combination of the mantle and paraaortic/spleen fields.**

In none of these more aggressive approaches did outcome benefit overweigh the additional toxicity. [49, 54-63] The most illustrative multi-centre trial is published by Fischer *et al*, showing no difference in outcome between CHOP and more complex 3rd generation chemotherapy regimens. [49] When treatment can be tailored not only to age, but also to other prognostic factors (IPI), new approaches yield better results than standard CHOP, however, long-term follow-up is needed.[52, 63-65, 70] In patients with poor-risk, aggressive NHL, addition of intensified CHOP before up-front, high-dose sequential therapy and ASCT is advocated, but for all the other newly diagnosed patients with advanced aggressive NHL (IPI<3), there is not enough proof for benefit of ASCT in the first line. [60-69]

For young patients with good-prognosis aggressive lymphoma, other approaches were introduced by the German High-Grade Non-Hodgkin's Lymphoma Study Group: CHOP

given every 2 weeks (CHOP-14) and the addition of etoposide, creating CHOEP-21 and CHOEP-14 (Table 8). CHOEP achieved better complete remission (87.6% versus 79.4%; P =.003) and 5-year event-free survival rates (69.2% versus 57.6%, p=0.004) than CHOP. Interval reduction improved overall survival in the multivariate analysis. Although the CHOEP regimens induced more myelosuppression, all regimens were well tolerated with standard granulocyte colony-stimulating factor (G-CSF) support. [70, 71] With standard G-CSF, CHOP and even CHOP-14, become feasible in elderly patients as well.[72,73]

Table 8. Polychemotherapy regimens by group

Eastern Cooperative Oncology Group	**CHOP:** 3-week interval of doxorubicin (50 mg/m^2) intravenously on day 1, cyclophosphamide (750 mg/m^2) intravenously on day 1, vincristine (1.4 mg/m^2) intravenously on day 1 (with the dose capped at 2.0 mg), and prednisone (100mg) orally from day 1 to day 5.
Groupe d'Etude des Lymphomes de l'Adulte	**ACVBP :** 4 induction courses given every 3 weeks of doxorubicin (75 mg/m^2) on day 1, cyclophosphamide (1200 mg/m^2) intravenously on day 1, vindesine (2 mg/m^2) on days 1 and 5, bleomycin (10 mg) on days 1 and 5, prednisone (60 mg/m^2) orally from day 1 to day 5, and intrathecal methotrexate (15 mg) on day 2, followed by a sequential consolidation therapy with 2 courses of intravenous methotrexate (3 g/m^2) plus leucovorin rescue, 4 courses of etoposide (300 mg/m^2) and ifosfamide (1500 mg/m^2) with mesna protection, and 2 courses of cytosine-arabinoside (100 mg/m^2) subcutaneously for 4 days, each consolidation course being administered at a 14-day interval.
European Organization for Research Treatment of Cancer	**CHVmP/BV:** 3 week interval of cyclophosphamide at a dose of 600 mg/m^2, doxorubicin at 50 mg/m^2, and teniposide at 60 mg/m^2 given intravenously on day 1, with prednisone at 40 mg/m^2 given orally on days 1, 2, 3, 4, and 5. On day 15, bleomycin at 10 mg (in total) and vincristine at 1.4 mg/m^2 (to a maximum of 2 mg) were given intravenously
German High-Grade NHL Study Group.	**CHOP-14:** CHOP given every 2 weeks **CHOEP-21** and **CHOEP-14:** CHOP with the addition of etoposide (100 mg/m2 days 1-3 and given every 2 or 3 weeks

The real improvement of outcome came with the association of anti-CD20 monoclonal antibody (rituximab) with chemotherapy. This association (R-CHOP) proved to be superior to chemotherapy alone in elderly patients with diffuse large B-cell lymphoma. The impressive results of this trial has provoked that additional rituximab has very quickly become a new standard of care in B-cell NHL. [74] Introduction of rituximab in other types of NHL can very well change the future standard in various NHL subtypes.

The role of radiotherapy in advanced stage aggressive NHL is highly controversial. Although the concept of combined modality treatment is proven effectively in early stage NHL and many other radiosensitive cancers, it has lost interest in advanced stage NHL, with the introduction of rituximab and possibilities of more aggressive approaches. Eight cycles of CHOP-like chemotherapy in combination with rituximab is seen as the standard, even for bulky disease or an incomplete response.[75]Although there could be a role for radiotherapy in

local control of bulky disease areas or residual disease, it is still a matter of debate whether improvement of outcome by additional radiotherapy outweighs toxicity. [75-78]

Response estimation

Guidelines for response assessment varied significantly between international cooperative groups (Table 9), and standardization was needed for comparison among clinical trials in NHL. To achieve this, two meetings were convened among international lymphoma experts representing medical haematology/oncology, radiology, radiation oncology, and pathology develop a uniform set of criteria for assessing response in clinical trials. [79] These criteria, known as the *Cheson-criteria*, were published in 1999 and included anatomic definitions of response, with normal lymph node size after treatment of 1.5 cm in the longest transverse diameter by CT scan. The minimum needed for response estimation after treatment is repetition of the CT scan of neck, thorax and abdomen (with description of disease diameters) and bone marrow biopsy (if initially positive). A designation of complete response unconfirmed (CRu) was adopted to include patients with a greater than 75% reduction in tumour size after therapy but with a residual mass, to include patients—especially those with large-cell NHL—who may not have residual disease. PET- and gallium scans were encouraged but as flow cytometric, cytogenetic, and molecular studies were not yet included in the response definitions (Table 10).[79] During the ASH Annual meeting of 2005 the members of the International Harmonization Project of the Competence Network Malignant Lymphoma presented revised guidelines, implementing the PET scan, which as said before, has become rapidly part of clinical disease evaluation (Table 11). [80, 81]

Table 9. Response criteria for NHL used by International Cooperative Groups

Group	Complete response (CR)	Partial response (PR)	Progressive disease (PD)
NCI of Canada Clinical Trials Group	Disappearance of all disease. No symptoms Must last 4 weeks or "unconfirmed CR"	50% or more decrease. No increase or new lesion Assessable disease stable or decreased Must last 4 weeks or "unconfirmed"	Increase by 25% in longest diameter, New lesion, Assessable disease progression
Cancer and Leukemia Group B	Disappearance of all disease. No symptoms. Biopsy suspicious residual nodes negative. Must last 4 weeks by physical examination *With residual abnormality:* Mediastinal or abdominal mass persists for two cycles after more than 50% decrease	More than 50% decrease of all lesions No new lesions Disappearance of symptoms, more than 30% decrease in liver, bone marrow normal liver function tests	More than 25% increase of any lesion compared with study baseline, New lesion
Eastern Cooperative Oncology Group	If Gallium scan was positive, now must be negative. Disappearance of all disease (normal nodes 1 x 1 cm ; nodes larger than 1 x 1 biopsy or observed x 3 months) negative. Normal liver/spleen; biopsy if was positive. Negative unilateral bone marrow. Must last at least 4 weeks	50% or more decrease, Liver decrease by 50% (below right costal margin), Spleen 5 cm or smaller or 50% decrease (below left costal margin) must become normal. Must last at least 4 weeks	Increase by > 25% or new lesion (Relapse: new disease after CR or PD after PR)
EORTC/Dutch Hemato-Oncology Group (HOVON)	Disappearance of all disease. Normal labs, x-rays, bone marrow. Persistent nodes biopsied or considered CR. Must last 4 weeks	50% or more decrease of all lesions, no new lesions No symptoms. No increase of more than 25% in any lesion with negative bone marrow. Must last 4 weeks	25% or more increase of one or more lesions. New lesion
Groupe d'Etude des Lymphomes de l'Adulte	Disappearance of all lesions (No palpable nodes, no mass larger than 1 cm in diameter on CT, no bone marrow involvement). Normal performance status Disappearance of initial biologic abnormalities	Regression of initial tumor mass (nodal, extranodal) by more than 50% or disappearance of all lesions but persistent bone marrow involvement with normal performance status and disappearance of initial biologic abnormalities	

Table 10. Response criteria for NHL as published by Cheson et al [79]

Response category	*Physical examination*	*Lymph nodes*	*Lymph node masses*	*Bone marrow*
CR	Normal	Normal	Normal	Normal
CRu	Normal Normal	Normal Normal	Normal More than 75% decrease	Indeterminate Normal or indeterminate
PR	Normal Normal Decrease in liver/ spleen	Normal 50% or more decrease 50% or more decrease	Normal 50% or more decrease 50% or more decrease	Positive Irrelevant Irrelevant
Relapse/progression	Enlarging liver/ spleen; new sites	New or increased	New or increased	Reappearance

Table 11. Guidelines +PET-based response designations based on the 1999-criteria (IWC) and PET findings [74,75]

Response designations	Description
Complete response (CR)	CR by IWC with a completely negative PET CRu, PR, or SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) 1.5 cm or more (1.0 cm or larger in the lungs) and negative BMB if positive prior to therapy
CR unconfirmed (Cru)	CRu by IWC with a completely negative PET but with an indeterminate BMB
Partial response (PR)	CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass SD by IWC with a positive PET at the site of a previously involved node/ nodal mass that regressed to less than 1.5 cm if previously larger than 1.5 cm, or smaller than 1 cm if previously 1.1-1.5 cm
Stable disease (SD)	SD by IWC with a positive PET at the site of a previously involved node/ nodal mass (i.e., residual mass)
Progressive disease (PD)	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion) PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of smaller than 1.5 cm (smaller than 1.0 cm in the lungs)

Abbreviations: IWC+PET, International Workshop Criteria plus positron emission tomography; CR, complete response; BMB, bone marrow biopsy; CT, computed tomography; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

As the 4 trials in this thesis originate from before the first international guidelines and far before the general use of gallium- and PET-scans, we need to emphasize here the EORTC

definitions as used during the years the 4 trials were performed and evaluated (1980-1999): The definition of **complete response (CR)** addresses to disappearance of all disease and B-symptoms. In EORTC protocols, no CRu distinction was made and a **partial response (PR)** was defined as 50-99% reduction of measurable disease, a *negative bone marrow* and disappearance of B-symptoms, whereas none of the lesions were allowed to have increased in size. In contrast, the patients classified as **failures (PD)** show less than 50% reduction of disease, a growing or new lesion or persisting bone marrow involvement.

Salvage treatment

In case of progressive or recurrent NHL, prognosis is very poor.[1] Second line (immuno) chemotherapy, radiotherapy or ASCT can be given in various orders, amongst others largely dependent on the condition and age of the patient. There is only one randomised study performed by the Parma Group showing that as compared with conventional chemotherapy, treatment with ASCT (after involved field radiotherapy in case of bulky disease ≥5cm) increases event-free (46% vs. 12% at 5 years, p=0.001) and overall survival (53% vs. 32% at 5 years, p=0.04) in patients with relapsing, but salvage-chemotherapy-sensitive aggressive NHL.[82] In this study, those (64%) patients obtaining at least a PR on 2nd line chemotherapy and without bone marrow or central nervous system involvement were randomized between conventional chemotherapy and BEAC (consisting of carmustine, etoposide, cytarabine, cyclophosphamide) followed by ASCT. Although only 109 selected young patients were randomized, accrued over a very prolonged period of time, ASCT is seen as the first choice of salvage treatment since this publication, if the condition of the patients allows this high dose approach.[82, 83]

In case of more than 50% but less than 99% (partial) response after 8 cycles in the first line, prognosis is generally considered as poor and patients are often seen as failures. Whereas in the past radiotherapy used to be given as first line salvage therapy, since the study by the Parma group, these patients are also frequently offered high dose chemotherapy followed by ASCT.[83, 84] If involved field radiotherapy after chemotherapy could convert a PR into a continuing CR, this would be a less toxic and therefore a much better option than ASCT. Up till now, only few groups analyzed the outcome of radiotherapy as first salvage treatment for PR in advanced aggressive NHL.[85, 86] All favored radiotherapy, but the numbers of PR patients were rather small. In the 4 EORTC studies involved field radiotherapy was prescribed as first salvage treatment (see guidelines below), also in case of PR after fully dosed first line chemotherapy. This policy offered us the opportunity to study the outcome related to salvage radiotherapy in PR patients in long-term follow-up (**chapter 3**).

The EORTC Lymphoma Group

In 1962 an international organisation was founded under Belgian law by eminent oncologists working in the main cancer research institutes of the EU countries and Switzerland. It was named 'Groupe Européen de Chimiothérapie Anticancéreuse' (GECA), and became the 'European Organisation for Research and Treatment of Cancer' (EORTC) in 1968. The aim of the EORTC was to perform extensive and comprehensive research accomplished through the multidisciplinary and multinational efforts of research scientists and clinicians from the

European continent working together. Within the EORTC, the Lymphoma Group, initially called the 'Radiotherapy-chemotherapy Group', was one of the first participating groups.

The EORTC NHL studies

The first trial in Non-Hodgkin's lymphoma (NHL) patients was designed by the group in 1975. The EORTC study 20751 consisted of a mixture of patients with NHL who received various combinations of first generation induction polychemotherapy regimens.[34, 35] In this trial, the role of histology, staging and polychemotherapy became apparent, and staging laparotomy was abandoned and radiotherapy fields and were indications reduced. In 1980, a second NHL trial (the EORTC study 20802) was started, guided by a panel of experts in lymphoma pathology and imaging. The CHVmP regimen (8 three-weekly cycles of cyclophosphamide, doxorubicin, teniposide, prednisone, was compared with the same scheme to which bleomycin and vincristine were added at mid-interval, day 15. This CHVmP/BV regimen resulted in a higher CR rate and a better overall survival at 5 and 10 years than the scheme without BV and became the EORTC standard. [51]

In 1985, the EORTC study 20855 was initiated randomizing CHVmP/BV versus ProMACE-MOPP, consisting of methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine and prednisone. Outcome was not significantly improved by this 'third-generation' regimen, which – moreover- yielded much more toxicity.[50]

In 1990, the EORTC study 20901 was started comparing 8 cycles of CHVmP/BV with 6 cycles of CHVmP/BV to which high dose consolidation chemotherapy (BEAC) was added followed by ASCT. Patients were evaluated after the first 3 CHVmP/BV cycles, and only those responsive (PR or CR) with a negative bone marrow at that time point, were randomized. The intention-to-treat analysis showed no difference between both arms with an overall survival at 5 years of 68% for the ASCT-arm versus 77% after 8 cycles of CHVmP/BV.[60]

In 1995, the EORTC 20932 study was initiated to evaluate the role of involved-field radiotherapy in case of CR after 8 cycles of CHVmP/BV. Unfortunately, this phase III trial had to be preliminary closed in 1998, because of poor accrual.

Guidelines of radiotherapy

Throughout the 4 EORTC trials, radiotherapy was prescribed by the involved field principle (Fig.2), covering only the nodal area or organ with proven NHL. [87-89] Radiotherapy was prescribed as consolidation treatment for patients in CR *only* in case of initially bulky disease (>5 cm) or slow response, defined as 50-99% response after the first 3 cycles (patients went of study protocol in case of less than 50% response) and consisted of 30 Gy (in fractions of 1.5-2 Gy) given to the involved fields covering the region of former bulky or slow responding disease. This consolidation radiotherapy was also noted as 'iceberg' irradiation, addressing the fact that it often covered the initial bulky area.

In case of PR after first line chemotherapy, radiotherapy was prescribed (involved field) as first salvage treatment to a dose of 40 Gy. If large fields were needed, a reduction of the field

focusing on the rest lesion was suggested for the last 4-10 Gy. For extranodal localizations other than bone marrow, the clinical target volume consisted of the pre-chemotherapy tumour volume with a 1.5 cm margin and the dose prescription was limited to 20-30 Gy, followed by a boost of 4-10 Gy after field reduction to reduce treatment related toxicity.

Update

Because the CHVmP/BV regimen (combined with radiotherapy in case of bulky disease or PR) had been consistently used in 4 successive EORTC trials (20802, 20805, 20901 and 20932) for patients with aggressive NHL (1980-1999) and all data were collected at the EORTC Data Centre in Brussels, Belgium, there was a unique possibility to update the almost 1000 patients enrolled, focussing on long-term efficacy and also late toxicity of this CHOP-like regimen. Since the introduction of the CHVmP/BV, there has been a lot of discussion about the benefit of the additional bleomycin and vincristine compared to CHOP, and many argued the possible extra toxicity of this regimen.

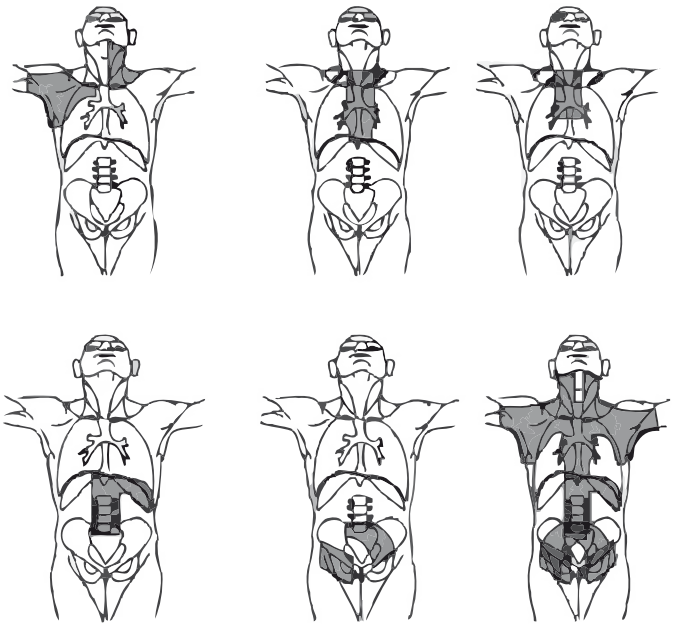


Fig. 2. Schematic representation of radiation fields for nodal areas described in detail by Aleman et al. in the EORTC 20884 quality control project (Int J Radiat Oncol Biol Phys. 2005;63:1184-90).

The update of long-term outcome and late effects was initiated in 2001 and in 2002 data were collected in the 55 participating centres in mainly the Netherlands, Belgium, France and Italy (see appendix). Of the 974 initially enrolled patients, outcome data were collected in 952 and late toxicity was scored in 757 patients (restricted to those with at least 6 months of follow-up). Response was estimated in all patients after 3, 6 and 8 cycles of first line chemotherapy and after additional radiotherapy and ASCT. Of the 974 enrolled patients, 842 were evaluated after 8 cycles: 63% were classified as CR and 28% as PR. More than half of all patients received salvage treatment, also scored in detail. Ultimately, a prolonged follow-up of twenty years could be evaluated (median 9.4 years).

According to the guidelines of the EORTC Lymphoma group (see above) almost half of all patients received additional radiotherapy. Thanks to the important contribution of radiotherapists in the EORTC Lymphoma group, all data on radiotherapy (dose, field size, and fractionation) were carefully documented. Thus, not only late efficacy and toxicity of the chemotherapy regimens used could be studied, but the separate contribution of radiotherapy as well.

Late effects

As outcome in aggressive NHL has improved by introduction of CHOP-like chemotherapy, therapy-related late effects of treatment have become an important issue.[49] The first reports on late complications (also noted late complications or sequellae), were published by e.g. Hancock *et al* and concerned patients with HL mainly treated with radiotherapy.[90-95] Follow-up in long-term survivors of HL showed that cumulative toxicity from treatment can rival the mortality from HL itself.[91] In addition to secondary malignancies,[90, 93, 95] delayed effects on the thyroid, reproductive, respiratory, cardiac and gastro-intestinal system were observed.[92, 93]After extended reviews on late effects after HL treatment,[96, 97] some reports have been published in patients with NHL as well. However, in none of the NHL reports could factors containing treatment details (dose, fields) and smoking history be taken into account.[98-102] Moreover, all different NHL categories were lumped together without central pathology review having been part of the selection process. Late complications in elderly (NHL) patients have never been well defined, as most data available originate from clinical trials limited to the age of 60 years. The 4 updated EORTC studies included a well defined NHL patient population of *all* adult ages (15-82 years old), homogeneously treated with CHOP-like chemotherapy during 1980-1999. Detailed information on type, dose and fields of first line and salvage treatment but also on smoking history, made it possible to evaluate the 24 types of late effects scored in the update in 2001, according to specific treatments and demographic factors (**chapter 4-6**).

Statistical considerations

The ideal comparison of different treatment regimens comes from observing groups that are otherwise equivalent. Clinical judgement, however, is almost certain to generate groups that differ systematically in baseline characteristics. Known factors can be accounted for in the analysis, but factors that are poorly specified or not yet known -such as new histology subtypes of NHL - cannot. Randomisation provides a method for obtaining equivalence between groups to be compared, but it does not ensure balance. Randomisation distributes baseline characteristics by chance and therefore most differences in outcome will be due to either chance or treatment. Standard statistical tests estimate the probability (*p-value*) whether differences in outcome, as observed, might be due to chance alone. The lower this p-value, the less plausible the observed difference will be caused by chance, and the more plausible that this difference is caused by the treatment.[103-108]

Sources of bias

Selection of the patients enrolled, defines the population to whom the results apply. Important characteristics include demographic data (e.g. age and sex), clinical characteristics (e.g. stage and histology), the performance status of the patients and other (possible) prognostic factors. The distribution of prognostic factors often influence outcome more than their subsequent treatment. Imbalance (expressed in a *p-value* by *Two-sided Fischer's exact test*) [105] of prognostic factors can have profound effects on the results.

Compliance refers to the extent to which a treatment is delivered as intended. It depends on the willingness of physicians and patients and is indirectly connected with (expected)

toxicity.

Crossover is a problem that influences the interpretation of long-term efficacy and occurs when patients allocated to one treatment subsequently receive the alternative for disease progression. Crossover changes the nature of the question A versus B into A followed by B versus B followed by A.

Co intervention occurs when treatments or medical support are administered that may influence outcome, but are not specified in the trial protocol. Because co interventions are not allocated randomly, they may be unequally distributed between groups.

Time is one of the factors most likely to induce bias in estimation of long-term efficacy. Changes in the spectrum of patients due to stage migration, better selection, more supportive care, or altered referral patterns can lead to spurious improvements in outcome that may be wrongly attributed to a new treatment. These changes over time are difficult to assess and adjust for in analyses. Such differences tend to favour the most recently treated group and can exaggerate the apparent benefit of new treatments.[106-108]

Comparison of survival

Clinical trials usually accrue patients over a prolonged period, often several years, and then follow them up for an additional period. Patients enrolled early are observed longer and are more likely to have died by the time of analysis. As not all patients will have died at the time of analysis, those patients still alive (and without event) are censored (definition of censoring is an incomplete observation of survival duration). Actuarial survival curves provide an estimate of survival distribution. The Kaplan-Meier method constructs an actuarial survival curve by graphically depicting a step function with the probability of surviving on the *y* axis and time on the *x* axis; with vertical drops occurring at each death. [102] The latter part of the survival curve is often of interest; however, this is also the most unreliable part of the curve, since it is based on the fewest observations. The size of any estimated difference should always be described, preferably with an indication of its precision. The precision is conveniently described by the **95% confidence interval (95% CI)**. [108] The usual interpretation of 95% CI is that we can be 95% confident that the true value lies within this range. These intervals are closely related to p values: a 95% CI that excluded a treatment effect of zero indicates a p value of less than 0.05; is regarded as *statistically significant*. Several tests are available for calculating *p* values for differences in survival distributions. The most commonly used is the log-rank test. [105, 108, 110]This test weights each occurrence (of death) equally, giving relatively great emphasis to late events. Differences in survival can be summarized in several ways: (1) the **absolute difference** in the proportion (%) of patients who are expected to be alive (or without another event) at a specific time-point (e.g. overall survival at 5 or 10 years). (2) The **hazard ratio (HR)** enhancing the ratio of instant (at one point in time) death rates after one treatment versus the other (probability of dying after treatment A divided by the probability of dying after B). (3) The **odds ratio** defined as the ratio of the odds of dying after one treatment versus the odds of dying after the other (probability of dying in a given period divided by the probability of surviving in that period. [98, 99]

The different ways of summarizing data are often confusing. When different summaries are presented in short time intervals, the hazard and odds ratio are almost identical. In case of a

HR of 1, probabilities of death (or another event) in both treatments are equal. When the HR >1, the probability of dying after B is smaller than after A, read as with A being the standard, the experimental treatment does better.

Retrospective research

In large prospective randomized trials, the likelihood of major imbalance is small and adjustments (stratifications) rarely affect the conclusions. Randomisation has balanced prognostic factors (known and unknown) between groups by chance (if the number of patients included is sufficient). [103, 104]However, randomized trials with limited number of patients, running over very long time-intervals or retrospective surveys are prone for several forms of bias. They can contain significant imbalance and adjustments are needed. Survival analysis can be adjusted, in principle, for any number of prognostic variables. The log-rank test allows stratification by for prognostic variables, but these have to be known (entered by hand) and made categorical (e.g. early vs. advanced, or younger than 60 vs. 60 years and older). [108]

Although all 4 EORTC-studies were large cohort randomized trials, the update-material has retrospectively been collected. Therefore all analyses are, per definition, biased. As the 4 trials covered almost two decades, the most dominant factor creating bias was time. Because the trials were successively performed, we stratified all survival analyses by trial to reduce this bias. We sought imbalance due to different prognostic factors to adjust for. However, selection (e.g. small differences in inclusion criteria) and compliance bias appeared present and many adjustments were needed. In these analyses the Cox's proportional hazards model is more appropriate. [111, 112] The model allows adjustment for continuous and time-dependent variables. In univariate analysis, the impact of one prognostic factor can be evaluated. Moreover, multivariate analysis can express the independent impact of this factor among other potential factors. [112] However, as unknown factors can still bias outcome, the only way to confirm retrospectively formed hypothesis is a prospective randomized trial.

Importance of competing risk analysis in analysis of late complications

If not survival, but occurrence of another event (for example the diagnosis of second cancer) needs to be investigated, the Kaplan-Meier method is also commonly used to arrive at an actuarial estimate.[108, 109] The curves start at zero and increase over time censoring those patients not (yet) diagnosed with second cancer at their last assessment or time of death. Because patients are censored at death, the estimate does not take into account competing causes of death. In other words, this method assumes that the risk of death from other causes has been completely removed. Consequently, the Kaplan-Meier estimates can give unexpected results. For example, if the longest (therefore the only) surviving patient is diagnosed with second cancer, the estimate increases to 100%. Confidence intervals and/or standard errors will increase as the number of patients at risk decreases and are therefore mandatory in Kaplan-Meier reports. [108, 110]

If in a patient population a great risk of death (as in our cohort of patients due to old age and poor prognosis NHL) is expected before running into the risk of the event (e.g. second cancer), the actuarial estimate of risk needs to take this competing risk of death into account,

otherwise risk will be overestimated (using the Kaplan-Meier method). This type of analysis has been described as a **competing risk analysis**, absolute cause-specific risk analysis and cumulative incidence.[113-116] The cumulative incidence estimates the percentage of patients diagnosed with second cancer at a certain time interval (e.g. 10 years of follow-up) in the presence of competing risk (e.g. death by any cause). This percentage, for example 4% at 10 years, means that if patients are treated today and we wait 10 years, 4% of these patients will be diagnosed with second cancer *before death from any other cause*.

Armitage *et al*.[117] stressed the difference in outcome by the use of the Kaplan-Meier versus the competing risk model in an article on leukaemia-risk in NHL patients with the following example: suppose a cohort of 100 patients is followed-up for 10 years. One patient is diagnosed with leukaemia 0.5 years after treatment of NHL and one additional patient is diagnosed every subsequent year until 9.5 years after treatment. In total 10 patients are diagnosed with leukaemia. Assume that 9 patients die every year before developing leukaemia (i.e. 90 patients die from competing risks, mainly NHL), and all patients are followed-up until death or leukaemia diagnosis. In this example, the competing risk analysis estimates a 10-years cumulative incidence of 10%. However, because the Kaplan-Meier estimate censors patients at death and these patients therefore contribute probability to later time points, the 10 years estimate is 33.3%. At the 5 years estimate the results are not yet very different, but the difference becomes clear as the number of patients at risk decreases (Fig. example).

Table example: Outcomes

Time (years)	No. of patients at risk	No. of patients diagnosed with MDS/AML	Kaplan-Meier estimate (%)	Cumulative incidence estimate (%)
0.0	100	0	0.00	0.00
0.5	96	1	1.04	1.00
1.5	86	1	2.19	2.00
2.5	76	1	3.48	3.00
3.5	66	1	4.94	4.00
4.5	56	1	6.64	5.00
5.5	48	1	8.67	6.00
6.5	38	1	11.21	7.00
7.5	26	1	14.62	8.00
8.5	16	1	19.96	9.00
9.5	6	1	33.30	10.00
10.0	1	0	33.30	10.00

Abbreviations: MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia.

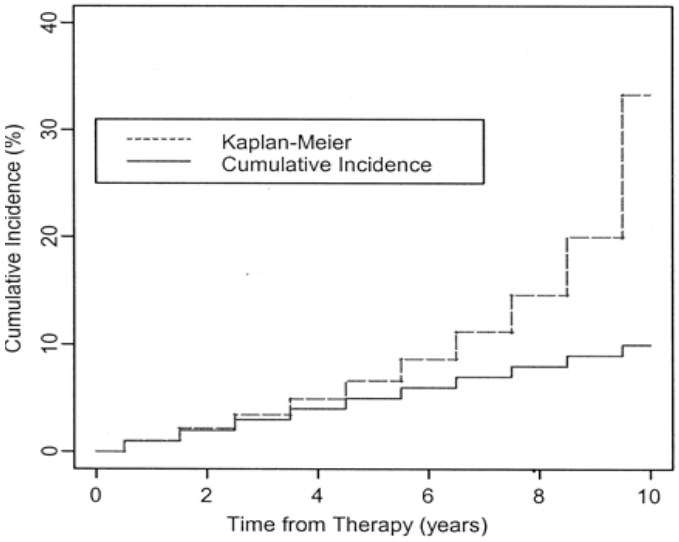


Fig. example: Kaplan-Meier estimate of actuarial incidence compared with cumulative incidence calculated using Andersen's competing risks analysis based on hypothetical data see above.

Standardized incidence risk

A better way of reporting late events is estimating the **relative risk**. Measures of relative risk compare rates of events among different cohorts of patients. If this is done to address risk to a certain type of treatment, this can only be informative if it is performed in the context of a randomized trial comparing those treatments. Better is to use the normal population as reference. However, for this type of comparison, incidence rates (number of first events per certain number of patients per time-interval) of the same event (for example lung cancer occurrence) in the normal population and the study cohort are needed, preferable covering the same distribution of age, sex, geographical region and calendar period. In this **person-years type of analysis**,[118] the ratio of observed (study cohort) and expected (normal population) number per event can be determined, and is addressed as **standardized incidence risk (SIR)**. The time-interval between end of treatment (for NHL) and diagnosis of the event (lung cancer) is expressed as person-years of follow-up. With the total length of the follow-up of the study cohort (for example 5,000 person-years) the expected cases can be estimated with the incidence rate in the normal population with the same duration of follow-up. In this example, estimating

an incidence of lung cancer in the Netherlands (95 per 100,000 inhabitants per year), will result in (5,000 x 90)/100,000=4.5 new lung cancers expected, while 6 are observed. The SIR is equal to 6/4.5 =1.3, addressing to a 30% rise lung cancer risk due to NHL treatment. In absolute numbers, this means that lung cancer risk in NHL patients rises from 0.9 to 1.2 per 10,000.

Risk estimation using crude incidence rates per country can be refined by several corrections: (1) Incidence rates differ between men and women, all analyses need to be done per sex. (2) Incidence rates change over time, for example the incidence of lung cancer in women has increased almost 2-fold in the last two decades, because of smoking habits. Therefore analyses need to be divided into 3 years reference calendar periods (1-1-1980 till 1-1-1984, 1-1-1984 till 1987 etc). (3) Incidence rates differ per age-category, the incidence of lung cancer increases almost ten-fold between the age of 20 and 70 years of age. To anticipate on this, the person-years need to be estimated per 5 years intervals and compared with the same 5 years age-categories of the reference rates.

When these 3 factors are integrated in the person-years analysis of the former example not 6 but 7.9 cases of lung cancer will be expected in the matched normal population and the SIR will be 6/7.9=0.8, e.g. less than one. Another way of describing late events is by the use of the term **absolute excess risk** (AER) calculated as the observed number of events in the study cohort minus the number expected, divided by number of person-years at risk, multiplied by 10,000. AER expresses the number of excess cases per 10,000 person-years diagnosed in the study group compared to the general population, and is seen as the best way to asses the burden of treatment related events in a patient population. In the lung cancer example will the AER be (6-4.5)/5000 x 10,000 = 30 uncorrected, and (6-7.9)/5000 x 10,000 = minus 3.8 after correction for sex and age. The uncorrected value addressed to 30 excess lung cancer cases, while in the proper corrected analysis slightly less cases of lung cancer were observed in the patient population compared to the general (Dutch) population.

As in all analyses, the precision of the estimated risk needs to be addressed and statistical significance will depend on the (95%) confidence limits. In person-years analyses numbers of events are often that small that the chance distribution is not symmetrically expected and non-symmetrical exact Poisson probabilities tests are needed.[119, 120] Population-based incidence rates needed for person-years analyses are scarce. Nation- and worldwide registration studies are ongoing, but only few general population-based registries are validated. For cancer incidences the National Cancer Institute's SEER (Surveillance Epidemiology and End Results) Program registers and provides population-based data in the United States. [121] In Europe, the European Network of Cancer Registries (ENCR) was established in 1989 within the framework of the 'Europe Against Cancer' program of the European Commission and tries to improve and combine cancer registries throughout Europe (used in **chapter 6**). [122] Combined efforts are mediated by the International Association of Cancer Registries (IACR), founded already in 1966, officially related with the World Health Organization since January 1979. [123] Registries, as exist for cancer, are for non-neoplastic disease even scarcer or inexistent (**chapter 4**). In the Netherlands a registry of non-neoplastic disease was started in 1971 at the Department of General Practice of the University of Nijmegen. This Continuous Morbidity Registration (CMRN) builds a database of every episode of disease presented

to the general practitioners in four affiliated practices, covering almost 1400 patients of all ages. [124-126]The relevance and limitations of this database are directly influenced by the Dutch health care system: nearly all residents have a GP and not only those seeking medical care. GPs receive all medical correspondence from attending physicians regarding their patients. Every GP has a stable practice population, being the official person to access specialized medical care. Hence, the dataset consists of the entire primary health care provided to the population as well as referrals for health care. The outcome of interest of the CMRN is estimating incidence of the most common diseases in the general population, according to age and gender over time. We used this database for risk estimation of cardiovascular disease (in **chapter 5**), but could therefore only estimate risk in patients treated in the Netherlands or Belgium.[118, 127-130]

Outline of this thesis

In **chapter 2** patient and treatment characteristics and long term efficacy of the CHVmP/BV regimen in the 4 successive EORTC studies in aggressive NHL are presented.

In **chapter 3** the sub-population of patients who obtained a PR after 8 cycles of first line chemotherapy is described. The role of involved field radiotherapy as salvage treatment is retrospectively evaluated.

In **chapter 4** the observed non-neoplastic late complications after treatment for aggressive NHL are presented.

In **chapter 5** the incidence of cardiovascular disease after NHL treatment is compared to normal population-based incidence rates.

In **chapter 6** the second cancer risk observed in the NHL-cohort is described.

Finally, in **chapter 7** the results of the estimation of long-term efficacy and late complications after treatment for aggressive NHL are summarized and discussed.

References

1. Aisenberg AC. Coherent view of non-Hodgkin's lymphoma. J Clin Oncol. 1995; 13:2656-75.
2. Tumours of haematopoietic and lymphoid tissue: In Jaffe ES, Harris NL, Stein H, Vardiman JW, et al: WorldHealth Organization Classification of Tumours. Lyon, France 2001: IARC Press.
3. Kruger GR, Grisar T, Lennert K, et al. Histopathological correlation of the Kiel with the original Rappaport classification of malignant non-hodgkin lymphomas. Blut. 1981 ;43:167-81.
4. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non- Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer 1982; 49: 2112-35.
5. Longo DL. The REAL classification of lymphoid neoplasms: One clinician's view. PPO Updates.1995;9:1.
6. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89:3909-18.
7. Poulsen CB, Borup R, Nielsen FC, et al. Microarray-based classification of diffuse large B-cell lymphoma. Eur J Haematol. 2005;74:453-65.
8. Bea S, Zettl A, Wright G, et al. Lymphoma/Leukemia Molecular Profiling Project. Diffuse large B-cell lymphoma subgroups have distinct genetic profiles that influence tumor biology and improve gene-expression-based survival prediction. Blood. 2005;106:3183-90.
9. Feuerhake F, Kutok JL, Monti S, et al. NFkappaB activity, function, and target-gene signatures in primary mediastinal large B-cell lymphoma and diffuse large B-cell lymphoma subtypes. Blood.

2005;106:1392-9.
10. Vandenberghe E. Mantle cell lymphoma. Blood Rev. 1994; 8:79.
11. Norton AJ, Matthews J, Pappa V, et al. Mantle cell lymphoma: natural history defined in a serially biopsied population over a 20-year period. Ann Oncol 1995;6:249.
12. Coiffier B, Hiddemann W, Stein H. Mantle cell lymphoma: a therapeutic dilemma. Ann Oncol 1995;6:208.
13. I. Teodorovic, S. Pittaluga, J.C. Kluin-Nelemans, et al. Efficacy of four different regimens in 64 mantle cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. J. Clin. Oncol.1995;**13:** 2819–2826.
14. Artimage JO, Greer JP Levine AM, et al. Peripheral T-cell lymphoma. Cancer 1989;63:158.
15. Rudiger T, Geissinger E, Muller-Hermelink HK. 'Normal counterparts' of nodal peripheral T-cell lymphoma. Hematol Oncol. 2006 Jun 19.
16. Pireli S, Falini B, Delsol G, et al. Lymphohistiocytic T-cell lymphoma. Histopathology 1990;16:383.
17. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood. 1999;93:3913-21.
18. ten Berge RL, Oudejans JJ, Ossenkoppele GJ, Meijer CJ. ALK-negative systemic anaplastic large cell lymphoma: differential diagnostic and prognostic aspects--a review. J Pathol. 2003;200:4-15.
19. ten Berge RL, Oudejans JJ, Ossenkoppele GJ, et al. ALK expression in extranodal anaplastic large cell lymphoma favours systemic disease with (primary) nodal involvement and a good prognosis and occurs before dissemination.J Clin Pathol. 2000;53:445-50.
20. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis.Oncologist. 2006;11:375-83.
21. Hummel M, Bentink S, Berger H, et al.Molecular Mechanisms in malignant lymphomas Network Project of the Deutsche Krebshilfe. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med. 2006;354:2419-30.
22. Dave SS, Fu K, Wright GW, et al. Lymphoma/Leukemia Molecular Profiling Project. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med. 2006;3542431-42.
23. Carbone P, Kaplan H, Musshof K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971;31:1860.
24. Lister T, Crowther D, Sutcliffe S, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease. J Clin Oncol. 1989;7:1630.
25. Mauch P, Leonard R, Skarin, et al. Improved survival following combined radiation therapy and chemotherapy for unfavorable prognosis stage I-II non-Hodgkin's lymphoma. J Clin Oncol 1985;3:1301.
26. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-94.
27. Castellino RA, Hilton S, O'Brien JP, Portlock CS: Non-Hodgkin's lymphoma: contribution of chest CT in the initial evaluation. Radiology 1996;199:129.
28. Kaplan W, Jochelson M, HermanT, et al. Gallium-67 imaging: a predictor of residual tumor viability and clinical outcome in patients with diffuse large-cell lymphoma J Clin Oncol1990;8:1966-69.
29. Wirth A, Seymour J, Hicks R, et al. Fluorine-18 fluorodeoxy-glucose positron emission tomography, gallium-67 scintigraphy and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. Am J Med 2002;112:262-66.
30. Ganem G, Thirion P. Role of radiotherapy in the treatment of adult nodal non-Hodgkin's lymphoma. Cancer Radiother. 1999;3:129-40.
31. Chen MG, Prosnitz LR, Gonzalez-Serva A, Fischer DB. Results of radiotherapy in control of stage I and II non-Hodgkin's lymphoma. Cancer. 1979;43:1245-54.
32. Kamath SS, Marcus RB Jr, Lynch JW, Mendenhall NP. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma.Int J Radiat Oncol Biol Phys. 1999;44:563-8.
33. Nissen NI, Ersboll J, Hansen HS, et al. A randomized study of radiotherapy versus radiotherapy plus

chemotherapy in stage I-II non-Hodgkin's lymphomas. Cancer. 1983;52:1-7.
34. Burgers JMV, Somers R, Quasim MM and van Glabbeke M, Report on the EORTC lymphoma trial 20751. Int.J. Radiat. Oncol. Biol. Phys.1983;9: 11–15.
35. Carde P, Burgers JM, van Glabbeke M, et al. Combined radiotherapy-chemotherapy for early stages non-Hodgkin's lymphoma: the 1975-1980 EORTC controlled lymphoma trial. Radiother Oncol. 1984;2:301-12.
36. Prestidge BR, Horning SJ, Hoppe RT. Combined modality therapy for stage I-II large cell lymphoma. Int J Radiat Oncol Biol Phys. 1988;15:633-9.
37. Monfardini S, Banfi A, Bonadonna G, et al. Improved five year survival after combined radiotherapy-chemotherapy for stage I-II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 1980;6:125-34.
38. Coltman CA, Dahlberg S, Jones SE, et al. CHOP is active in thirty percent of patients with large cell lymphoma: a twelve year Southwest Oncology Group follow up. In: Skarin AT, ed. Advances in Cancer Chemotherapy:Update on Treatment for Diffuse Large Cell Lymphoma. New York, NY: ParkRow; 1986: 710-77.
39. Longo DL. Combined modality therapy for localized aggressive lymphoma: enough or too much? J Clin Oncol. 1989;7:1179-81.
40. Longo DL, Glatstein E, Duffey PL, Ihde DC, Hubbard SM, Fisher RI, Jaffe ES, Gilliom M, Young RC, DeVita VT Jr.Treatment of localized aggressive lymphomas with combination chemotherapy followed by involved-field radiation therapy. J Clin Oncol. 1989;7:1295-302.
41. Longo DL.Chemotherapy for advanced aggressive lymphoma: more is better ...isn't it? J Clin Oncol. 1990;8:952-5.
42. Arriagada R, Cosset JM, le Chevalier T, Tubiana M. The value of adjunctive radiotherapy when chemotherapy is the major curative method. Int J Radiat Oncol Biol Phys. 1990 ;19:1279-84.
43. Shenkier TN, Voss N, Fairey R, et al. Brief chemotherapy and involved-region irradiation for limited-stage diffuse large-cell lymphoma: an 18-year experience from the British Columbia Cancer Agency.J Clin Oncol. 2002;20:197-204.
44. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med. 1998;339:21-6.
45. Miller TP, Leblanc M, Spier C, et al. CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: Update of the Southwest Oncology Group (SWOG) randomized trial. Blood 2001;98:724a.
46. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484.J Clin Oncol. 2004;22:3032-8.
47. Reyes F, Lepage E, Ganem G, et al. Groupe d'Etude des Lymphomes de l'Adulte (GELA). ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma.N Engl J Med. 2005;352:1197-205.
48. van der Maazen RW, Noordijk EM, Thomas J, et al. Combined modality treatment is the treatment of choice for stage I/IE intermediate and high grade non-Hodgkin's lymphomas. Radiother Oncol. 1998;49:1-7.
49. Fisher RI, Gaynor ER, Dahlberg S,et al.Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993;328:1002-6.
50. R. Somers, P. Carde, J. Thomas et al. EORTC study of non-Hodgkin's lymphoma: phase-III study comparing CHVmP-VB and ProMACE-MOPP in patients with stages II, III and IV intermediate and high-grade lymphoma. Ann. Oncol. 1994;5: S85–S89.
51. Meerwaldt JH, Carde P, Somers R, et al. Persistent improved results after adding vincristine and bleomycin to a cyclophosphamide/hydroxorubicin/Vm-26/prednisone combination (CHVmP) in stage III-IV intermediate- and high-grade non-Hodgkin's lymphoma. The EORTC Lymphoma Cooperative Group.Ann Oncol. 1997;8 Suppl 1:67-70.
52. Coiffier B, Reyes F; Groupe d'Etude des Lymphomes de l'Adulte. Best treatment of aggressive non-Hodgkin's lymphoma: a French perspective. Oncology (Williston Park). 2005;19 (4 Suppl 1):7-15.
53. Gordon LI, Harrington D, Andersen J, et al. Comparison of a second-generation combination chemotherapeutic

regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med. 1992;327:1342-9.

54. Linch DC, Smith P, Hancock BW, et al. A randomized British National Lymphoma Investigation trial of CHOP vs. a weekly multi-agent regimen (PACEBOM) in patients with histologically aggressive non-Hodgkin's lymphoma.Ann Oncol. 2000;11 Suppl 1:87-90.
55. Jerkeman M, Anderson H, Cavallin-Stahl E, et al. CHOP versus MACOP-B in aggressive lymphoma--a Nordic Lymphoma Group randomised trial. Ann Oncol. 1999;10:1079-86.
56. Montserrat E, Garcia-Conde J, Vinolas N, et al. CHOP vs. ProMACE-CytaBOM in the treatment of aggressive non-Hodgkin's lymphomas: long-term results of a multicenter randomized trial.(PETHEMA: Spanish Cooperative Group for the Study of Hematological Malignancies Treatment, Spanish Society of Hematology). Eur J Haematol. 1996;57:377-83.
57. Somers R, Carde P, Thomas J, et al. EORTC study of non-Hodgkin's lymphoma: phase-III study comparing CHVmP-VB and ProMACE-MOPP in patients with stages II, III and IV intermediate and high-grade lymphoma. Ann. Oncol. 1994;5: S85–S89.
58. Koppler H, Pfluger KH, Eschenbach I, et al. Randomised comparison of CHOEP versus alternating hCHOP/IVEP for high-grade non-Hodgkin's lymphomas: treatment results and prognostic factor analysis in a multicentre trial. Ann Oncol. 1994;1:49-55.
59. Meyer RM, Quirt IC, Skillings JR, et al. Escalated as compared with standard doses of doxorubicin in BACOP therapy for patients with non-Hodgkin's lymphoma. N Engl J Med. 1993;329:1770-6.
60. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: Randomized phase III EORTC study. J Natl Cancer Inst 2001;93:22-30.
61. Haioun C, Lepage E, Gisselbrecht C, et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: A study of 464 patients—Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1994;12:2543-2551.
62. Santini G, Salvagno L, Leoni P, et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: Results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. J Clin Oncol 1998;16:2796-2802.
63. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: Final analysis of the prospective LNH87-2 Protocol-A Groupe d'Etude des Lymphomes de l'Adulte Study. J Clin Oncol 2000;18:3025-3030.
64. Tilly H, Lepage E, Coiffier B, et al. Groupe d'Etude des Lymphomes de l'Adulte. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood. 2003;102:4284-9.
65. van Imhoff GW, van der Holt B, Mackenzie MA, et al.Impact of three courses of intensified CHOP prior to high-dose sequential therapy followed by autologous stem-cell transplantation as first-line treatment in poor-risk, aggressive non-hodgkin's lymphoma: comparative analysis of Dutch-Belgian Hemato-Oncology Cooperative Group Studies 27 and 40.J Clin Oncol. 2005;23:3793-801.
66. Nademanee A, Schmidt GM, O'Donnell MR, et al. High-dose chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy during first complete remission in adult patients with poor-risk aggressive lymphoma: A pilot study. Blood 1992;80:1130-1134.
67. Freedman AS, Takvorian T, Neuberg D, et al. Autologous bone marrow transplantation in poor-prognosis intermediate- grade and high-grade B-cell non-Hodgkin's lymphoma in first remission: A pilot study. J Clin Oncol 1993;11:931-936.
68. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997;336:1290-1297.
69. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med 2004;350:1287-1295.
70. Pfreundschuh M, Trumper L, Kloess M, et al. German High-Grade Non-Hodgkin's Lymphoma Study

Group. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood. 2004;104:626-33.

71. Pfreundschuh M, Trumper L, Kloess M, et al.Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood. 2004;104:634-41.
72. Gomez H, Mas L, Casanova L, Pen DL, et al. Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: identification of two age subgroups with differing hematologic toxicity. J Clin Oncol. 1998;16:2352-8.
73. Rigacci L, Nassi L, Alterini R, et al. Dose-dense CHOP plus rituximab (R-CHOP14) for the treatment of elderly patients with high-risk diffuse large B cell lymphoma: a pilot study. Acta Haematol. 2006;115:22-7.
74. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42.
75. Shipp MA, Klatt MM, Yeap B, et al. Patterns of relapse in large-cell lymphoma patients with bulk disease: implications for the use of adjuvant radiation therapy.J Clin Oncol. 1989;7:613-8.
76. Aviles A, Delgado S, Fernandez R, et al. Combined therapy in advanced stages (III and IV) of follicular lymphoma increases the possibility of cure: results of a large controlled clinical trial. Eur J Haematol. 2002;68:144-9.
77. Wilder RB, Rodriguez MA, Ha CS, et al. Bulky disease is an adverse prognostic factor in patients treated with chemotherapy comprised of cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy for aggressive lymphoma. Cancer. 2001;91:2440-6.
78. Aviles A, Neri N, Delgado S, Perez F, et al. Residual disease after chemotherapy in aggressive malignant lymphoma: the role of radiotherapy.Med Oncol. 2005;22:383-387.
79. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas: NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244-1253.
80. Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphomas From the Members of the International Harmonization Project (IHP) of the Competence Network Malignant Lymphoma, Blood (ASH Annual Meeting Abstracts)2005; 106: 18.
81. Malik E. Juweid, Gregory A. Wiseman, et al. Cheson Response Assessment of Aggressive Non-Hodgkin's Lymphoma by Integrated International Workshop Criteria and Fluorine-18–Fluorodeoxyglucose Positron Emission Tomography Journal of Clin Onc 2005;21:4652-4661.
82. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545.
83. Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on high-dose therapy with hematopoietic stem-cell transplantation in aggressive non-Hodgkin's lymphomas: report of the jury.Ann Oncol. 1999 ;1:13-9.
84. Vose JM: High-dose chemotherapy and hematopoietic stem cell transplantation for relapsed or refractory diffuse large-cell non-Hodgkin's lymphoma. Ann Oncol. 1998;9 :S1-3.
85. Wilder RB, Rodriguez MA, Tucker SL, et al: Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. Int.J of Rad Oncol Biol Phys 2001;50:743-749.
86. Schlembach PJ, Wilder RB, Tucker SL, et al: Impact of involved field radiotherapy after CHOP-based chemotherapy on stage III-IV, intermediate grade and large-cell immunoblastic lymphomas. Int J Radiat Oncol Biol Phys 2000;48:1107-1110.
87. Mendenhall NP.The role of radiation in the management of Hodgkin's disease: an update. Cancer Invest. 1999;17:47-55.
88. Rosenberg SA, Kaplan HS: Clinical trials in the non-Hodgkin's lymphomata at Stanford University experimental design and preliminary results. Br J Cancer. 1975;31 S2: 456-464.

89. Aleman BM, Girinsky T, van der Maazen RW, et al. Quality control of involved-field radiotherapy in patients with advanced Hodgkin's lymphoma (EORTC 20884). Int J Radiat Oncol Biol Phys. 2005;63:1184-90.
90. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst.1993; 85:25-31.
91. Hancock SL, Hoppe RT. Long-Term Complications of Treatment and Causes of Mortality After Hodgkin's Disease. Semin Radiat Oncol. 1996;6:225-242.
92. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA.1993; 270:1949-55..
93. Bhatia S, Robinson LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med.1996; 334:745-751.
94. Hoppe RT. Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol 8 Suppl 1997;1:115-8.
95. Armitage JO. Long-term toxicity of the treatment of Hodgkin's disease. Ann Oncol 1998;9 Suppl 5:S133-6.
96. Swerdlow A.J, van Leeuwen F.E. Late effects after treatment for Hodgkin's Lymphoma. in Dembo A.J, Linch D.C, Lowenberg B (eds): Textbook of Malignant Hematology. Abingdon, United Kingdom, Taylor & Francis, 2005:753-68.
97. Van Leeuwen FE, Travis LB: Second cancers, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott Williams & Wilkins, 2005; 2575-2602.
98. Haddy TB, Adde MA, McCalla J, et al: Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol.1998; 6:2070-9.
99. Andre M, Mounier N, Leleu X, et al: Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 2004; 103:1222-8.
100. Aviles A, Diaz-Maqueo JC, Garcia EL,et al. Late lethal events in patients with diffuse large B cell lymphoma, a review of 714 patients treated in a single centre. Leuk Lymphoma 2001; 42:631-7.
101. Mudie N.Y, Swerdlow A.J, Higgins C.D, et al. Risk of secondary malignancy after Non-Hodgkin's Lymphoma: a British cohort study. J Clin Oncol 2006; 24:1-6
102. Travis L.B, Curtis R.E, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's Lymphoma. J Natl Cancer Inst 1993; 85:1932-37.
103. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer. 1976;34:585-612.
104. Peto R, Pike MC, Armitage P, et al.Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples.Br J Cancer. 1977;35:1-39.
105. Freeman DH. Applied categorical data analysis. Vol.79 of Statistics: Textbooks and monographs. New York: Marcel Dekker, 1987
106. Sacks ST, Glantz SA. Introduction to biostatistics. An annotated bibliography for medical researchers. West J Med. 1983;139(5):723-9.
107. Breslow N. Comparison of survival curves, in Buyse ME (ed): Cancer clinical trials methods and practice. Oxford, UK, Oxford Medical Publications, 1988, 382-406.
108. Greenwood M. The errors of sampling of the survivorship tables. Reports on Public Health and Statistical subjects.HMSO, Londen,1926;33.
109. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc.1958; 53:457.
110. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163-70.
111. Cox DR. Regression models and life-table. J R Stat Soc 1972, 34,187-220.
112. Tibshirani R. A plain man's guide to the proportional hazards model. Clin Invest Med. 1982;5(1):63-8.
113. Kalbfleisch JD, Lawless JF. Likelihood analysis of multi-state models for disease incidence and mortality. Stat Med. 1988;7:149-60.

114. Jiang H, Chappell R, Fine JP. Estimating the distribution of nonterminal event time in the presence of mortality or informative dropout. Control Clin Trials. 2003;24:135-46.
115. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1988; 16:1141-54.
116. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999 Mar 30;18(6):695-706.
117. Armitage JO, Carbone PP, Connors JM, et al. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21:897-906.
118. Van Leeuwen FE, Travis LB: Second cancers, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott Williams & Wilkins, 2005; 2575-2602.
119. Liddell FD. Simple exact analysis of the standardised mortality ratio. Journal of Epidemiology and Community Health 1984;38:85-88.
120. Silcocks P. Estimating confidence limits on a standardised mortality ratio when the expected number is not error free. Journal of Epidemiology and Community Health 1994;48:313-317.
121. Ries LAG, Harkins D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Eisner MP, Horner MJ, Howlader N, Hayat M, Hankey BF, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2003*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2003/, based on November 2005 SEER data submission, posted to the SEER web site, 2006.
122. J.E. Tyczynski, E. Démaret, D.M. Parkin. Standards and Guidelines for Cancer Registration in Europe, IARC Technical Publication No. 40, IARC Press, 2003.
123. J.Ferlay, F. Bray, R. Sankila, D.M. Parkin. EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union 1998, version 5.0. IARC Cancer Base No. 4. Lyon, IARC Press, 1999; http://www.encr.com.fr/encr.htm.
124. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978-1994. Eur Heart J.1998; 19:429-434.
125. Lisdonk van de EH, Bosch van den WJHM, Huygen FJA, Lagro-Jansen ALM. Ziekten in de huisartspraktijk (3e druk). Maarssen: Elsevier/Bunge;1999.
126. Gijssen R, Poos MJJM: Achtergronden en details bij cijfers uit huisartsenregistraties. Gezondheid en ziekte\ziekte en aandoeningen\hartvaatstelsel\coronaire hartziekten. Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven, RIVM; 2003. http:www.rivm.nl/vtv/object_document/o3171nl7964.html.
127. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, et al: Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet 2000; 355:675-87.
128. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, et al, for the WHO MONICA Project: Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. Lancet 2000; 355: 688-700.
129. Empana JP, Ducimetiere P, Arveiler D, et al: Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J. 2003; 21:1903-11.
130. Paul I, Bilge A, Bolly F, Boland J, et al: Pilot study for the registration of acute myocardial infarction in the Liege area (Belgium). Rev Epidemiol Sante Publique.2001; 5:423-9.

Chapter 2

Long term efficacy of the CHVmP/BV regimen used for aggressive non-Hodgkin's lymphoma across three randomized EORTC-trials

E.C. Moser, E.M. Noordijk, M.M.B. van Glabbeke, I. Teodorovic, C. de Wolf-Peeters , P. Carde, J.W. Baars, U. Tirelli, J.M.M. Raemaekers and J.C. Kluin-Nelemans

European Journal of Cancer 40;474-480, 2004.

Abstract

We analysed data of 936 newly-diagnosed patients with advanced aggressive non-Hodgkin's lymphoma (NHL) treated in 3 randomized EORTC-trials performed between 1980 and 1999 (median follow-up 8.7 (0.2-20.4) years). The CHOP-like regimen CHVmP/BV (cyclophosphomide, doxorubicin, teniposide and prednisone with bleomycin and vincristine at mid-interval), was compared with CHVmP (CHVmP/BV without bleomycin and vincristine), ProMACE-MOPP (methotrexate, doxorubicin, cyclophosphamide, etopside, mechlorethamide, vincristine, procarbazine and prednisone) and CHVmP/BV with additional autologous stem-cell transplantation, respectively. Overall, CHVmP/BV resulted in a better long-term outcome with 63% complete responses being observed and an overall survival (OS) of 59% and 43% at 5 and 10 years, respectively. Remarkably, OS after CHVmP/BV improved across trials, even after stratifying for the International Prognostic Index. This finding could not be directly related to better salvage treatment during the last decade. Selection bias appeared responsible: stepwise corrections for small differences in inclusion criteria eliminated the OS difference especially when histology subgroups were studied. This systemic review underlines the risk of retrospective subset analyses and the bias introduced when recent studies are compared to older ones.

Introduction

Patients with advanced aggressive non-Hodgkin's lymphoma (NHL) can be effectively treated with multi-agent chemotherapy. Although the majority (55-80%) of patients below the age of 65 will reach a complete remission (CR) after 6 to 8 courses of CHOP-like chemotherapy, less than 50% will be cured. Many trials have been performed, also within the European Organisation for Research and Treatment of Cancer (EORTC)[1], introducing new drugs and more aggressive approaches, aiming to improve the outcome in this group of NHL patients. Since 1980, the CHVmP/BV scheme, which contains cyclophosphamide, doxorubicin, teniposide and prednisone combined with vincristine and bleomycin, has been consistently used in 3 consecutive EORTC phase III trials[2-5]. Combining these trials resulted in a unique chance to review efficacy of this regimen over a 20-year period. We observed remarkably large differences across trials in long-term outcome. By presenting our analyses, we want to underline the risk of comparing recent studies with older ones, showing the bias introduced by retrospective subset analyses.
Patients and Methods

Eligibility

Between 1980 and 1999, 936 newly diagnosed and untreated patients with advanced aggressive NHL were registered in three prospective phase III randomized EORTC-trials (20802, 20855 and 20901). Follow up was missing or incomplete in 23 patients. Altogether, 913 patients could be analyzed. All three trials were designed for intermediate or high grade NHL classified by the Working Formulation (WF) as D-J[6]. Histological classification (Table 1) was performed by the local pathologist and reviewed by a Lymphoma Pathology Panel after randomization. The panel was supervised by the same person across all trials, who reviewed all cases in the WF classification, so no new pathology review was performed for our systemic review. All cases, including 52 low-grade NHL, 22 Lymphoblastic and 15 Burkitt's lymphoma after panel review, were included in the analysis. In all patients, the WHO performance status was less than three. The inclusion criteria regarding age and Ann Arbor stage were somewhat different throughout the three trials. Advanced disease was defined in trial 20802 as Ann Arbor stage III or IV, while in 20855 stages II was also accepted. In trial 20901, patients with stage I bulky (>10 cm) were included as well, if histology was classified as WF high grade. Age was limited to 15-70 years in trials 20802 and 20855. Initially in 20901 the upper-limit was 60 years, which was expanded during the run of the trial to 65 years.

International Prognostic Index (IPI)

The IPI [7] was computed (adding up points in case of age >60 years, WHO performance >1, Ann Arbor stage >II, raised LDH and more than one extranodal location at time of diagnosis) in 867 patients and classified in low-, low/intermediate-, intermediate/high- and high-risk groups. In 46 patients, information on one or more of the five factors was missing (Table 2).

Treatment and review design

In the first trial (20802), 195 patients were randomized between 1980 and 1986 and 189 could be included in our systemic review. The CHVmP/BV regimen consisted

of 8 cycles of cyclophosphamide, doxorubicin, teniposide and prednisone with bleomycin and vincristine in every cycle at mid-interval. This regimen was compared with the old standard without the addition of bleomycin and vincristine (CHVmP). In the next trial (20855) running from 1986 till 1990, 430 patients were randomized and 413 patients could be analyzed. The new CHVmP/BV standard was compared with ProMACE-MOPP, also 8 cycles. This third generation scheme consisted of doxorubicin, cyclophosphamide, mechlorethamine, vincristine, procarbazine and prednisone. Trial 20901 ran between 1990 and 1999 and compared 8 cycles CHVmP/BV with 6 cycles followed by autologous stem cell transplantation (ASCT) after consolidation with the BEAC regimen (BCNU, VP16, Ara-C and cyclophosphamide). In contrast to the previous two trials where upfront randomization took place, here the patients were only randomized if either a partial response with a negative bone marrow or a complete response was obtained after the third cycle (n=194). In the systemic review, all 311 patients registered in trial 20901 were analyzed (194 randomized and 117 non-randomized) together with the 189 and 413 randomized patients from 20802 and 20855. In all three trials, radiotherapy was recommended for initial bulky disease (>5 cm) and partial response after 3 cycles. In 336 patients, areas of bulky disease and/or slow response were irradiated after protocol chemotherapy; a dose of 30-40 Gy was given.

Response criteria

Response was evaluated after 3 cycles and at the end of protocol therapy according to the WHO criteria[8]. Complete response was defined as disappearance of all symptoms and lesions, including normalization of blood values, X-rays and bone marrow. Partial response was defined as a decrease of at least 50% in the product of two perpendicular diameters in all lesions, a negative bone marrow, and disappearance of symptoms. Progression was defined as an increase in size of at least 25% of one or more lesions or the occurrence of new lesions or symptoms. When not qualified for one of these three criteria, response was defined as stable disease. Protocol treatment was stopped in case of no change or progression after three cycles of chemotherapy.

Statistical analysis

Statistical analyses were performed according to the 'intention to treat principle' including all patients randomized in 20802 and 20855 or registered in 20901. Outcome was evaluated in terms of overall survival, stated as the time between the date of randomization and the date of death from any cause. Patients who were still alive when last contacted were censored at the date of last follow-up. For the patients who were not randomly assigned, the overall survival was calculated as the time between the date of registration and the date of death. Survival curves were estimated by the use of the Kaplan-Meier method [9, 10] and compared by the use of log-rank tests [11, 12]. All statistical tests used were two sided.

Table 1. Histological characteristics according to the Working Formulation

Working Formulation.	cell type	20802	20855	20901	Total
Low grade	A, B, or C	31 (16%)	16 (4%)	5 (2%)	52 (6%)
Intermediate grade	D	5 (3%)	23 (5%)	11 (3%)	39 (4%)
	E	23 (12%)	52 (13%)	20 (6%)	95 (10%)
	F	22 (12%)	45 (11%)	17 (5%)	83 (9%)
	G	57 (30%)	181 (44%)	165 (53%)	404 (44%)
High grade	H	15 (8%)	45 (10%)	4 (1%)	64 (7%)
	I (Lymphoblastic)	14 (8%)	7 (2%)	1 (1%)	22 (2%)
	J (Burkitt)	6 (3%)	7 (2%)	2 (1%)	15 (2%)
Unclassified		16 (8%)	37 (9%)	86 (28%)	145 (15%)
	total	189	413	311	913

Results

Long-term efficacy

Out of 913 patients with advanced aggressive NHL 55% and 47% were still alive at respectively 5 and 10 years (median follow-up of 8.7 years). The median survival was 7.3 (0.2-20.4) years, with 388 (42%) patients still alive at the time of analysis. Protocol treatment was stopped in 168 (18%) patients after 3 cycles, showing no response; from the patients who continued protocol treatment, 63% of the patients treated with CHVmP/BV obtained a complete remission.

Randomized trials

Trial 20802 was updated with a median follow-up of 18 years. The previously established benefit of adding bleomycine and vincristine to CHVmP persisted in the prolonged follow-up, showing overall survival at 10 years of 34 vs. 21% (p=0.009, Hazard Ratio (HR) of 1.56). When CHVmP/BV (trial 20855) was compared with ProMACE-MOPP (median follow up 12 years), a trend towards a better OS after CHVmP/BV was seen, but it was not statistically significant by log-rank testing (OS at 10 years 42 vs. 37%, p=0.064, HR 1.27). However, in earlier analyses[3,4] it was clear that ProMACE-MOPP commensurate with more (acute) toxicity. Comparing the CHVmP/BV scheme without or with ASCT in patients randomized after 3 cycles, in trial 20901, did not show any benefit of this more aggressive approach even at the median follow-up of 8 years. Overall survival at 10 years was 70 vs. 67% (p=0.455 HR 1.22).

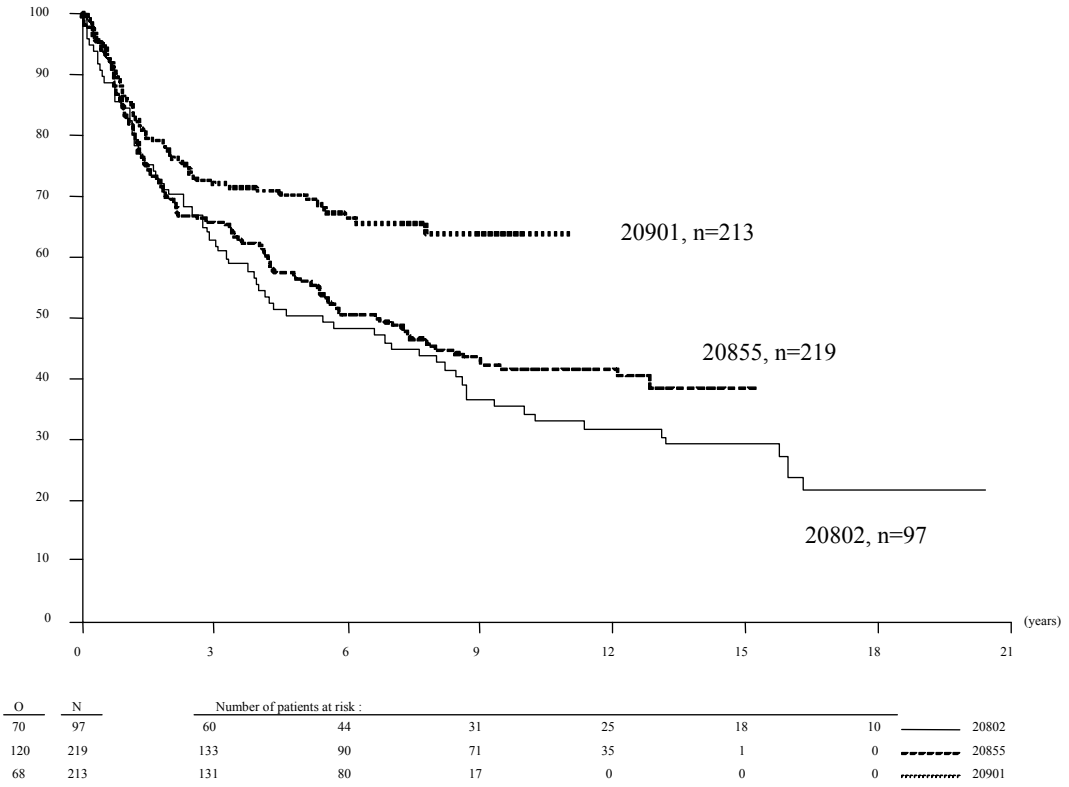
Table 2. Distribution of International Prognostic Index (IPI) factors

	20802 (n=189)	***20855 (n=413)***	20901 (n=311)
Age			
≤60	131 (69%)	267 (65%)	303 (97%)
>60	58 (31%)	146 (35%)	8 (3%)
Ann Arbor Stage			
1-2	5 (3%)	145 (35%)	122 (39%)
3-4	177 (97%)	268 (65%)	189 (61%)
WHO performance			
≤1	147 (78%)	342 (83%)	270 (87%)
>1	34 (18%)	67 (16%)	41 (13%)
missing	8 (4%)	4 (1%)	0
LDH			
normal	141 (75%)	385 (93%)	142 (46%)
elevated	39 (21%)	21 (5%)	157 (50%)
missing	6 (4%)	7 (2%)	12 (4%)
Extra nodal locations			
0-1 locations	172 (91%)	375 (91%)	293 (94%)
>1	11 (6%)	37 (8.5%)	18 (6%)
missing	6 (3%)	2 (0.5%)	0
IPI			
IPI low	78 (41%)	251 (60%)	176 (57%)
IPI low/intermediate	68 (36%)	44 (11%)	81 (26%)
IPI intermediate/high	25 (13%)	98 (24%)	40 (13%)
IPI high	5 (3%)	7 (2%)	2 (1%)
missing	13 (7%)	13 (3%)	12 (4%)

Variation in outcome of CHVmP/BV-arm

From the 529 patients treated with the CHVmP/BV regimen, 59% and 43% were still alive at respectively 5 and 10 years. Comparison of results across trials showed a remarkable improvement in overall survival over time (p=0.001, HR 0.73, Fig.1). Our first hypothesis was that this variation could be due to improved rescue treatment in the last decade. Almost half of the patients (48%) in all three trials progressed or had recurrent disease and 82% of them received salvage treatment. Out of various initial rescue regimens, the ones containing ASCT resulted in a better OS (p=0.011 HR 1.26) and were more often used in patients from the 20901 trial. When long-term outcome after rescue treatment in 20901 was compared to 20802 and 20855, a trend in favor of 20901 was seen (p=0.066 HR 1.27). However, when the fact if rescue treatment was given was not taken into account (1/3 did not receive this treatment) and all patients who failed after protocol treatment were analyzed across trials: no difference was observed anymore (p=0.887). In summary, the reason for variation of outcome across trials could not be explained by improved salvage treatment alone.

Fig.1 Comparison of overall survival after CHVmP/BV across trials



Role of selection

An obvious explanation for the better outcome of patients in trial 20901 could have been the late randomization resulting in selection of good responders. Therefore, we included for further analysis all registered patients in this trial and not just the randomized patients. However, the overall survival remained superior in trial 20901 to the other two (earlier) trials. Differences in inclusion criteria might still have been responsible for a better outcome in time. We assumed that the IPI should correct for differences in stage and age, but when the 430 patients with a low and low/intermediate risk profile treated with CHVmP/BV were selected, the patients from trial 20901still did significantly better (p=0.002 HR 0.72). In contrast, for patients with an IPI of 3 or more (n=99), survival was poor irrespective of which trial they had been included (p=0.34; HR 0.82). Therefore, we corrected stepwise for the seemingly small differences in inclusion criteria age and stage (Table 3, Fig.2). Patients were relatively younger in trial 20901 (upper age limit was initially 60 years and later extended to 65 years; however, only 8 patients >60 years were finally included) and stages I bulky and II were excluded in trial 20802. We re-analyzed the data by matching for age (60 or younger) and stage (III and IV). Comparing outcome in trial 20901 to 20802 and 20855, while matching for age did give a raise in Hazard Ratio (HR), but still showed a difference in OS (p=0.032, HR 0.77). Matching for age and stage raised the HR

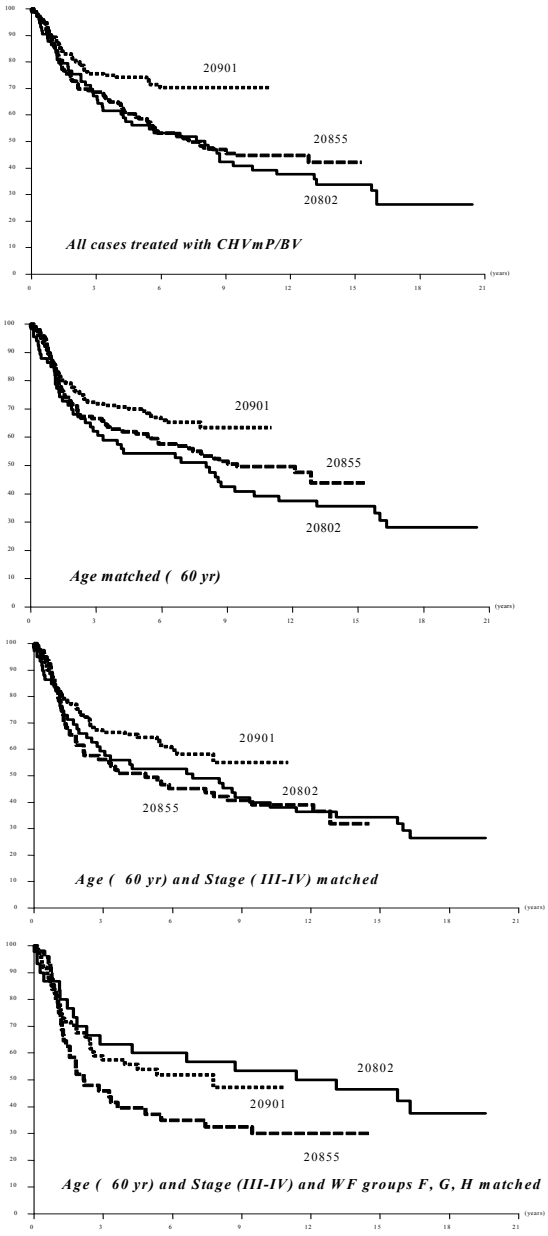
and p-value further and no significant difference in OS was seen anymore (p=0.195, HR 0.85). After comparing the patients aged 60 years or younger, and stage III or IV and with histology classified as group F, G or H (diffuse, mixed, small and large cell or diffuse large cell or large cell immunoblastic NHL) by the Working Formulation the HR normalized to 1.02 (p=0.265). Altogether, we observed a significant improvement of outcome across trials that persisted when grouping patients with the same IPI-risk profile. However this difference disappeared when patients were matched for age, stage and histology (Table 3).

Table 3. Comparison of overall survival across trials; patients were all treated with the same CHVmP/BV regimen across trials and matched for age, stage and histology after comparison by IPI low-intermediate and intermediate-high risk

Comparison	**Trial**	**% alive at 5 years**	**95% CI**	**Log-rank p-value**	**Hazard Ratio**	**90% Hazard Confidence**	**Number of patients**
CHVmP/BV in:	20802	50%	40-60				97
	20855	56%	49-63				219
	20901	70%	64-77	p=0.001	0.73*	0.61	213
CHVmP/BV	20802	56%	44-68				73
if IPI low/intermediate-risk	20855	59%	51-66				178
	20901	74%	68-81	p=0.001	0.71*	0.63	173
CHVmP/BV	20802	32%	13-51				24
if IPI intermediate/high-risk	20855	44%	29-60				41
	20901	54%	38-70	p=0.473	0.83*	0.70	40
CHVmP/BV	20802	32%	42-66				66
if age ≤ 60yrs	20855	44%	53-69				141
	20901	54%	64-76	p=0.032	0.77*	0.71	208
CHVmP/BV	20802	53%	40-65				59
if age ≤ 60 *and* stage >2	20855	49%	38-61				79
	20901	65%	56-73	p=0.195	0.84*	0.68	133
CHVmP/BV	20802	60%	42-77				30
if age ≤ 60 *and* stage >II *and*	20855	37%	23-51				48
WF pathology F,G or H	20901	54%	42-66	p=0.265	1.02*	0.78	74

WF=Working Formulation; CHVmP/BV= 8 cycles of cyclophosphamide, doxorubicin, teniposide and prednisone with bleomycin and vincristine *patients in trial 20901were compared to patients in trial 20802 and 20855

Fig.2 Comparison of overall survival after CHVmP/BV across trials after matching by IPI (1), age (2), age and stage (3) and or age *and* stage *and* histology (last)



Discussion

Several different regimens have been applied in patients with advanced aggressive NHL. Fisher *et al* [13] compared third generation regimens (m-BACOD, ProMACE-CytaBOM, MACOP-B) with classical CHOP, and found no difference in outcome between all four regimens. We had similar findings when we compared ProMACE-MOPP, as third generation regimen, with the EORTC based CHVmP/BV regimen. However, by adding bleomycine and vincristine to the CHVmP scheme, we improved survival outcome significantly. Fisher[13] described a **3** years overall survival of 54% for the CHOP regimen. In our update we found an overall survival of 59% at **5** years with CHVmP/BV. Although the only way to prove the superiority to CHOP can be found in a randomized trial, CHVmP/BV seems at least equivalent to classical CHOP. We observed large differences in outcome of the CHVmP/BV regimen across trials. Rescue treatment and, more importantly, age and stage distribution biased the difference in outcome across trials. This biased difference persisted when stratifying by the IPI risk profile. When the distributions of the 5 factors of the IPI (especially age and stage) are not balanced within a population, sub-set analysis using this prognostic tool can be very misleading. Besides the factors found in the IPI-score, histology plays an important role in the prognosis of NHL patients as well[14]. The classification of NHL by histology has changed considerably over the last two decades, which is the same period our data were collected. In our trials, NHL categories had been defined as intermediate- and high-grade histology following the Working Formulation, including subgroups like Lymphoblastic and Burkitt's lymphoma. Other subgroups like anaplastic large cell lymphoma were not yet recognized as a different entity in the Working Formulation. Subgroups like these have to be seen as entities with there own prognostic impact[15]. An overview of the revised pathology showed that a considerable number of patients were ineligible because of (low-grade) histology. When analyzing accordingly to the 'intention to treat principle' these cases were included. In the subset analysis, we selected cases using the Working Formulation (F, G and H) aiming to create a more homogeneous category of aggressive NHL, in part comparable with the diffuse large B-cell category of the REAL and WHO classifications. Evidently, our goal was not to define outcome within histology sub-groups, but to stress the fact that diversity in histology can also lead to selection bias and the importance of the correct diagnosis. Altogether, interpretation of retrospective sub-group analyses and comparison of recent trials with previous ones, have to be done with great prudence. Patients with advanced aggressive NHL differ not only in the factors defined within the IPI, but also in histology. They often progress and undergo rescue treatment, which also influences outcome. Implementation of new therapeutic approaches should only be done after prospective randomized confirmation within a selected subset, being the only way to prevent selection bias in this heterogeneous group of patients.

References

1. Raemaekers JM, Kluin-Nelemans JC, Teodorovic I, et al. The achievements of the EORTC Lymphoma Group. Eur J Cancer 2002, 38, S107-13 (suppl 4).
2. Carde P, Meerwaldt JH, van Glabbeke M, et al. Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non- Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. The EORTC Lymphoma Group. Ann Oncol 1991, 2, 431-5.
3. Somers R, Carde P, Thomas J, et al. EORTC study of non-Hodgkin's lymphoma: phase III study comparing CHVmP-VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. Ann Oncol 1994, 5, 85-9.
4. Meerwaldt JH, Carde P, Somers R, et al. Persistent improved results after adding vincristine and bleomycin to a cyclophosphamide/hydroxorubicin/Vm-26/prednisone combination (CHVmP) in stage III-IV intermediate- and high-grade non-Hodgkin's lymphoma. The EORTC Lymphoma Cooperative Group. Ann Oncol 1997, 8, 67-70 (suppl 1).
5. Kluin-Nelemans JC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 2001, 93, 22-30.
6. Kluin-Nelemans JC. Indications for early autologous stem cell transplantation in aggressive lymphoma. Ann Hematol 2001, 80, B121-2, (suppl 3).
7. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non- Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. Cancer 1982, 49, 2112-35.
8. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993, 329, 987-94.
9. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva, Switzerland, 1997.
10. Breslow N. Comparison of survival curves, in Buyse ME (ed): Cancer clinical trials methods and practice. Oxford, UK, Oxford Medical Publications, 1988, 382-406.
11. Cox DR. Regression models and life-table. J R Stat Soc 1972, 34,187-220.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966, 50, 163-70.
13. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993, 328, 1002-6.
14. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997, 89, 3909-18.
15. Teodorovic I, Pittaluga S, Kluin-Nelemans JC, Meerwaldt JH, et al. Efficacy of four different regimens in 64 mantle-cell lymphoma cases: clinicopathologic comparison with 498 other non-Hodgkin's lymphoma subtypes. European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group. J Clin Oncol 1995, 13, 2819-26.

Chapter 3

Impact of involved field radiotherapy in partial response after doxorubicin-based chemotherapy for advanced aggressive non-Hodgkin's lymphoma

E.C. Moser, J.C. Kluin-Nelemans, P. Carde, J. H. Meerwaldt, U. irelli, B.M.P. Aleman, J. Baars, J.Thomas, M.M.B. van Glabbeke and E.M. Noordijk

Int J Radiation Oncology Biol Phys, 2006 Aug. 1

Abstract

Purpose: Whether salvage therapy in patients with advanced aggressive non-Hodgkin's lymphoma (NHL) in partial remission (PR) should consist of radiotherapy or autologous stem cell transplantation (ASCT) is debatable. We evaluated the impact of radiotherapy on outcome in PR patients treated in 4 successive EORTC-trials for aggressive NHL.

Patients and Methods: Records of 974 patients (1980-1999) were reviewed regarding initial response, final outcome and type and timing of salvage treatment. After 8 cycles of doxorubicin-based chemotherapy, 227 NHL patients were in PR and treated: 114 received involved field radiotherapy, 16 ASCT, 93 second-line chemotherapy and four were operated. Overall (OS) and progression-free survival (PFS) after radiotherapy were estimated (Kaplan-Meier method) and compared with other treatments (log-rank). Impact on survival was evaluated by multivariate analysis (Cox proportional-hazards model).

Results: The median PFS in PR patients was 4.2 years and 48% remained progression-free at 5 years. Half of the PR patients converted to a complete remission (CR). After conversion, survival was comparable to patients directly in CR. Radiotherapy resulted in better OS and PFS compared to other treatments, especially in patients with low to intermediate International Prognostic Index-score, bulky disease or nodal disease only. Correction by multivariate analysis for prognostic factors like stage, bulky disease and number of extranodal locations, showed that radiotherapy was clearly the most significant factor affecting both OS and PFS.

Conclusion: This retrospective analysis demonstrates that radiotherapy can be effective for patients in PR after fully dosed chemotherapy; assessment in a randomized trial (radiotherapy vs. ASCT) is justified.

Introduction

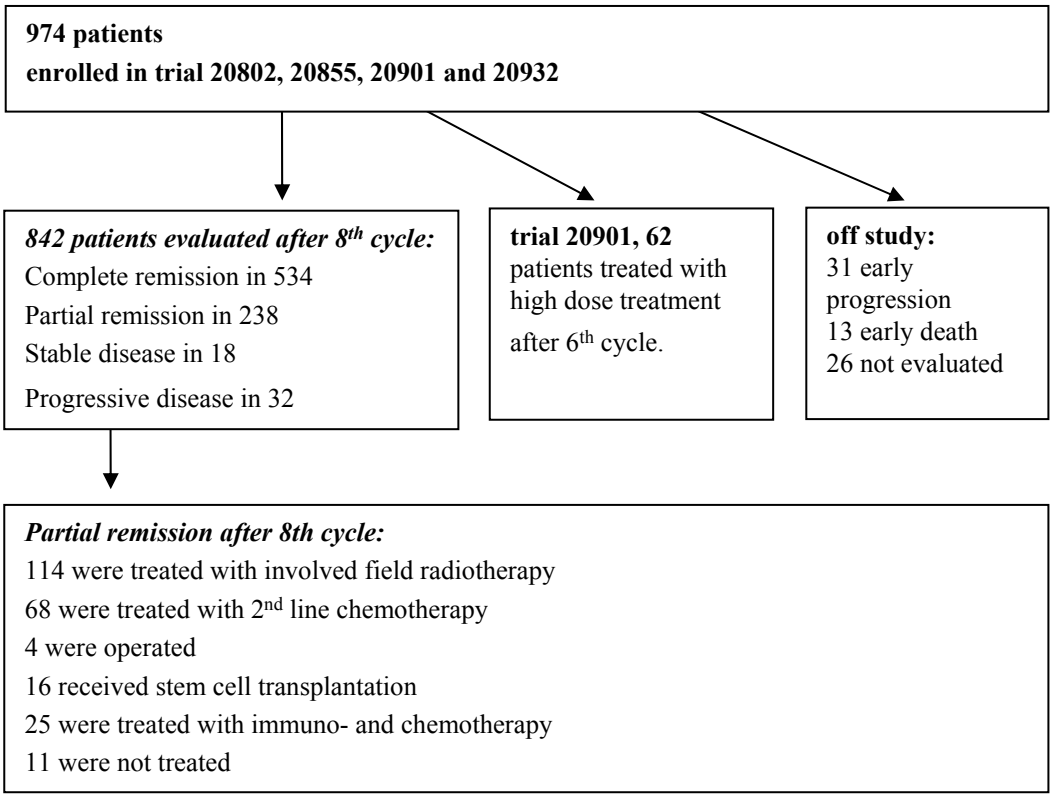
First line treatment for patients with advanced aggressive non-Hodgkin's lymphoma (NHL) consists of multi-agent chemotherapy. The majority of patients below the age of 65 will reach a complete remission (CR) after 6 to 8 courses of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)-based therapy.[1] Although first line treatment has been improved over the last 10 years, not all patients obtain a CR after full dose chemotherapy.[2, 3] In case of partial response (PR), defined as 50-99% reduction in size of the largest lesion by the International Working Group guidelines,[4] prognosis is generally considered as poor and patients are often grouped together with those with refractory disease or early progression. Whereas in the past radiotherapy used to be given as first line salvage therapy, nowadays, this group is frequently offered high dose chemotherapy followed by autologous stem cell transplantation (ASCT).[5, 6] If involved field radiotherapy after chemotherapy could convert a PR into a continuing CR, this would be a less toxic[7-9] and therefore a much better option than ASCT. Up till now, only few groups analyzed the outcome of radiotherapy as first salvage treatment for PR in advanced aggressive NHL.[10-12] All favored radiotherapy, but the numbers of PR patients were rather small. During the last decades, the EORTC (European Organization of Research and Treatment of Cancer) Lymphoma Group treated PR patients as a separate cohort in their protocols for advanced aggressive NHL. In all trials involved field radiotherapy was prescribed as first choice of salvage treatment. This policy offered us the opportunity to study the outcome related to salvage radiotherapy in a cohort of 227 patients with advanced aggressive NHL who were treated for PR after 8 cycles of doxorubicin-based chemotherapy and had longstanding follow-up.

Patients and Methods

Patients

From 1980 through 1999, 974 patients with untreated advanced aggressive NHL were enrolled in four succeeding EORTC-trials (respectively 20802, 20855, 20901 and 20932) and were followed yearly by the local investigators.[13-15] In 2002, all patient records were revised and information on disease status, date, location and type of relapse (if any), type and timing of salvage treatment, details of radiotherapy (fields and doses) and date with cause of death were updated. At start of 1st line treatment, the International Prognostic Index-score (IPI) was calculated (accumulating points for age over 60, stage III-IV of disease, poor performance status, raised lactate dehydrogenase levels (LDH) and more than one extranodal NHL localization).[16] Location, size and type of disease were documented at start, after 3, 6, and 8 cycles, and in case of progression or successive recurrence. Bulky disease was defined as NHL lesions larger than 5 cm in all dimensions. All pathology was centrally reviewed. Approval of the study was obtained from the EORTC Protocol Review Committee and from all local institutions. Informed consent was provided according to the Declaration of Helsinki.

Fig.1 Number of patients enrolled and treated according to estimated response



Treatment

All patients received doxorubicin-based chemotherapy as 1st line treatment. The CHVmP/BV regimen was standard in all four trials, consisting of 8 three-weekly cycles of cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin and vincristine. Two other regimens were given: CHVmP (CHVmP/BV without bleomycin and vincristine) and ProMACE-MOPP (consisting of methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine and prednisone). [13, 14] In the 20901 EORTC trial, patients were randomized between 8 cycles of CHVmP/BV versus 6 followed by high dose therapy and ASCT. [15] We restricted our analyses for this study to those patients who received 8 cycles of doxorubicin-based chemotherapy as 1st line treatment (excluding those patients treated with 6 cycles and ASCT). According to EORTC Lymphoma Group guidelines, all PR patients should receive involved field radiotherapy in all 4 EORTC protocols. All radiotherapy treatments were retrospectively reviewed and field, dose, and dates were registered, but also alternative treatments were registered in detail, including type and date of second-line treatments. Interval between the end of the 8th cycle and the start of salvage treatment was estimated. Salvage therapy was categorized as radiotherapy vs. other salvage treatments and analyzed if given within 8 weeks after the end of the 8th cycle. Regarding study-protocol, radiotherapy consisted of 40 Gy in fractions of 1.5-2 Gy, 5 times a week. In case of nodal disease, involved field regions were given as defined by Kaplan and Rosenberg[17]. If large fields were needed, a reduction of the field was suggested

for the last 4-10 Gy. For extranodal localizations other than bone marrow, the clinical target volume consisted of the pre-chemotherapy tumor volume with a 1.5 cm margin and was dose prescription limited to 20-30 Gy, followed by a boost of 4-10 Gy after field reduction to reduce treatment related toxicity.

Response definitions

Response was defined as complete if all documented disease had disappeared. PR was defined as 50-99% reduction in the largest diameter of every measurable lesion on the conventional CT scan, accompanied by a negative bone marrow (biopsy proven if initially positive). To confirm PR, gallium or 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography imaging (PET) was advised. For extranodal disease, the protocols prescribed confirmation of PR by cytology or histology. Treatment was considered to have failed in case of persistent bone marrow involvement and/or less than 50% reduction of initial disease or progressive disease. Response to treatment was documented by the local investigator, verified by tumor measurements on CT scans and authorized by the study coordinators (2-4 weeks) after the 3rd, 6th and 8th chemotherapy cycle and (4-6 weeks) after radiotherapy.

Statistical Analysis

Overall survival (OS) and progression-free survival (PFS) were calculated according to the Kaplan-Meier method. [18] Survival was measured from the start of 1st line chemotherapy till death from any cause or date of last contact. PFS was calculated from the start of 1st line chemotherapy till progression, relapse or death by any cause or last contact. As the aim of this study was evaluation of outcome in PR patients treated with radiotherapy (addressed as the radiotherapy group), PR patients treated with other modalities than radiotherapy within 8 weeks after the 8th cycle of first line chemotherapy were grouped as a reference (addressed as other salvage treatment group). The number of patients directly treated with ASCT was too small (n=16) to make a comparison of radiotherapy vs. ASCT salvage. Two-sided Fischer's exact test was used to estimate balance between the radiotherapy vs. the other salvage group at start of 1st line treatment and in case of progression or recurrence.[19] The reference group was used (compared to the radiotherapy group by log-rank testing) in the evaluation of several factors (initial IPI, bulky disease, bone marrow and other extranodal disease involvement). Finally, impact of salvage radiotherapy on survival and PFS among other factors (gender, age, stage of disease, performance status, elevated LDH, number of extranodal localizations and largest tumor size at start of first line treatment, type of first line chemotherapy, and salvage ASCT) was evaluated by multivariate analysis (Cox proportional-hazards model), stratified by trial. [20]

Results

Out of 974 patients enrolled in trial 20802, 20855, 20901, and 20932, 842 received 8 cycles of 1st line chemotherapy, see Figure 1. After 8 cycles, 534 obtained a CR and 238 a PR . The patient characteristics of the 227 PR patients, who were treated within 8 weeks, are given in Table 1.

Table 1. Characteristics of NHL patients in PR after fully dosed chemotherapy at start of first line treatment

	Total n=227	salvage radiotherapy n=114	other salvage n=113	*p-value
Age				
younger than 60	180	92	88	NS
60 years or older	47	22	25	
Ann Arbor stage				
I-II	62	36	26	p=0.05
III-IV	167	78	87	
LDH				
normal	146	72	74	NS
elevated	81	41	40	
WHO				
0-1	200	105	95	NS
2-4	27	9	18	
Nodal disease involvement				
axillary	82	37	45	NS
cervical	126	61	65	NS
mediastinal	223	114	109	NS
hilar	34	17	17	NS
abdominal	109	44	65	0.02
inguinal	80	36	44	NS
iliacal	66	30	36	NS
Bulky disease involvement				
none	129	68	61	NS
mediastinal	29	18	11	NS
abdominal	57	24	33	0.04
other	12	4	8	NS
Extranodal disease involvement				
none	91	50	41	0.01
1 location	86	42	44	NS
>1 locations	50	22	28	NS
bone marrow	107	47	60	0.02
liver/spleen	100	41	59	0.03
lung	45	17	28	0.05
bone	11	4	7	NS
Waldeyer's ring	99	53	46	NS
other	65	34	31	NS
1st line Chemotherapy				
CHVmP	23	18	5	0.003
CHVmP/BV	143	94	55	
ProMACE-MOPP	61	52	3	
International Prognostic index				
Low	107	60	47	0.03
Low/Intermediate	81	38	43	
High/Intermediate	28	13	15	
High	11	3	8	

LDH=lactate dehydrogenate, WHO=performance status classified by the World Health Organization *Two-sided Fischer's exact

Eleven patients were not treated, mainly because of age or poor performance status. The median age of the PR patients was 58 years (range 18-76) at start of treatment, 78% had stage III-IV NHL at diagnosis. Most PR patients (82%) had an IPI-profile of low to intermediate risk (2 or less) at start of initial therapy. From the 227 PR patients treated, 114 received involved field radiotherapy (median dose 40 Gy, range 34-48 Gy), 68 second-line chemotherapy, four

surgery, 16 ASCT (all after high dose chemotherapy conditioning; no total body irradiation had been given), and 25 a combination of immunotherapy and chemotherapy. Comparing PR patients treated with radiotherapy with those who received other salvage treatment, patients who were not irradiated had higher Ann Arbor stages (p=0.05), more often extranodal localizations of disease (p=0.02) at start of first line chemotherapy, a higher IPI-risk profile (p=0.03) and more often bulky abdominal disease (Table 1). Salvage radiotherapy was more commonly (p=0.003) used in the earlier trials after the CHVmP and ProMACE-MOPP regimens; rescue ASCT was introduced later on.

Out of the 227 PR patients, 100 (44%) obtained a CR after first salvage treatment; 69 (61%) after radiotherapy, 12 (75%) after ASCT, 12 (21%) after chemotherapy, all four after surgery and eight (32%) after immuno- and chemotherapy. The median follow-up after start of first line treatment for all patients was 9.2 years (range 0.2-20.4) and in case of PR 6.1 years (range 0.8-19.8). Half of the PR patients were still alive at 5 years after treatment, 48% remained disease-free at 5 years and 37% at 10 years (median PFS 4.2 years). As expected, patients who obtained a CR after 8 cycles had a better survival than those in PR (OS at 5 years 59% vs. 51%, p=0.02). If PR patients obtained a CR by first salvage treatment, outcome became comparable to the patients directly in CR (OS at 5 years 57%). The 5-year OS of PR patients after radiotherapy was 61%, after ASCT 68% and after second line chemotherapy 32%, respectively. When the radiotherapy and the other salvage group were compared, both OS (p=0.001) and PFS (p=0.006) were significantly better after radiotherapy (Fig.2). Given the differences between both patient groups, we compared OS and PFS per IPI-risk group and adjusted for bulky and extranodal disease and stratified by trial (Fig.4). OS for patients in PR with a low to intermediate IPI risk was significantly better after radiotherapy than after other treatment (consisting mainly of chemotherapy). In patients with high to intermediate risk (IPI>2), outcome was poor regardless of the type of salvage. When analyzing outcome per Ann Arbor stage, all stages did significantly better after radiotherapy than after other treatment. Patients with nodal disease only and with bulky lesions benefited most from radiotherapy. The most common extranodal localization of NHL at start of chemotherapy was bone marrow involvement (Table 1). If these patients obtained a PR (by definition according to the EORTC protocols without bone marrow involvement after therapy), outcome was also good if radiotherapy was given as first salvage therapy (Fig.5). About half (n=127) of the PR patients did not reach a CR after salvage and progressed (Table 2). Many progressed in the same nodal region as before. However, if involved field radiotherapy was given, local control was significantly better (p=0.01) than after salvage chemotherapy.

On multivariate analysis radiotherapy appeared as the most significant factor affecting both OS (Fig.3, p=0.001, hazard ration (HR) 2.0 95% CI 1.18-3.45) and PFS (p<0.001, HR 2.4 95% CI 1.51-3.93).

Fig. 2a Overall survival in PR-patients: radiotherapy vs. other salvage treatment (p=0.001)

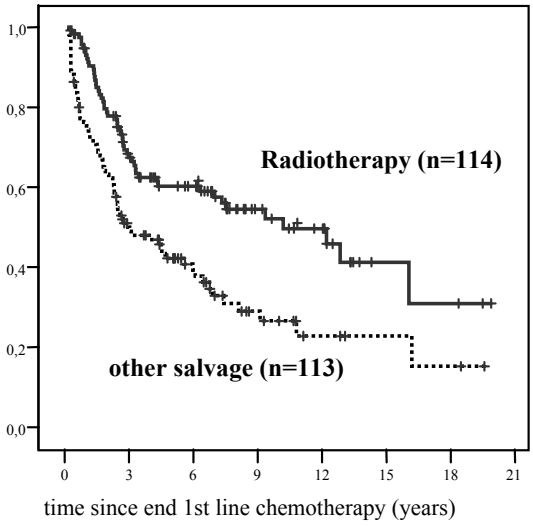


Fig. 2b Progression-free survival in PR-patients: radiotherapy vs. other salvage treatment (p=0.006)

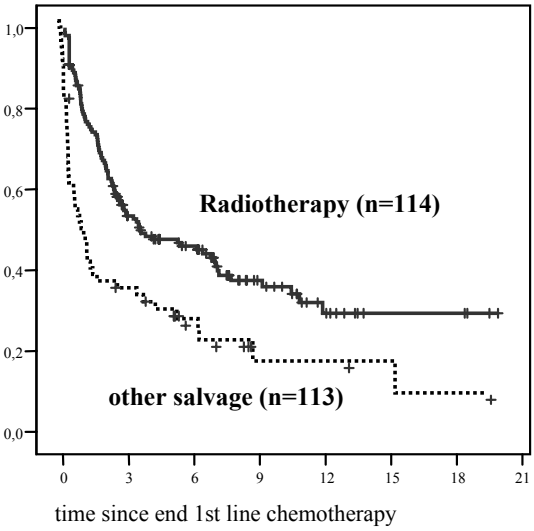


Fig.3 Cox regression on factors influencing overall survival in PR patients, stratified by trial

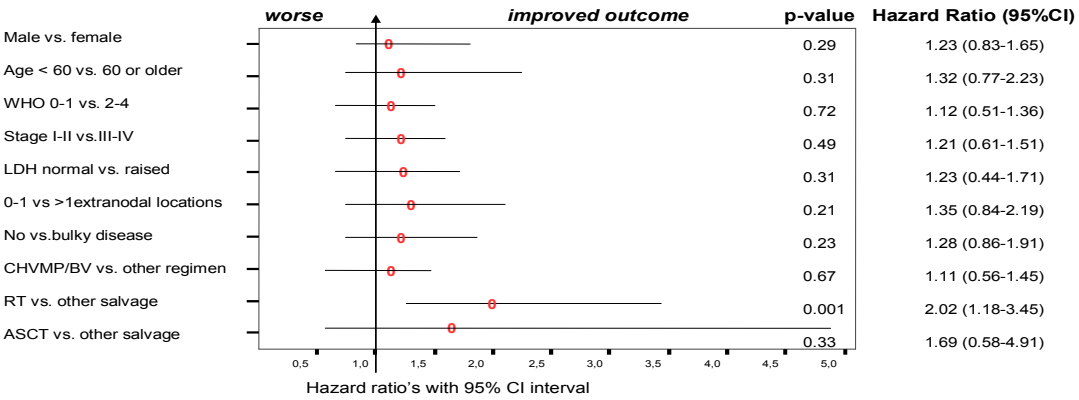


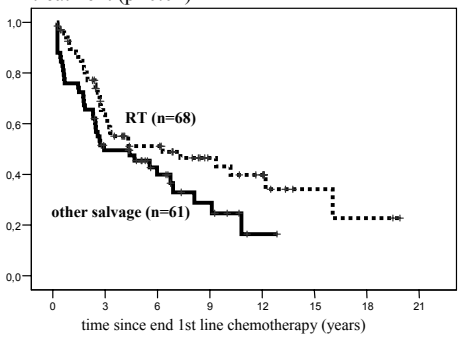
Table 2. PR patients not in CR after first salvage

	total n=127	**salvage radiotherapy n=58**	**other salvage n=69**	***p-value**
Type of progression				
nodal	42	17	25	NS
extranodal	24	13	11	
both	61	28	33	
Location nodal progression				
same region	53	18	35	p=0.01
other region	49	27	22	
both	25	13	12	
Initial bulky disease				
no	75	39	36	NS
yes	52	19	33	
Location extranodal progression				
bone marrow	21	8	13	NS
liver/spleen	38	13	25	NS
lung	18	9	9	NS
bone	17	11	6	NS
central nervous system	18	7	11	NS
other	15	10	5	NS
Initial extranodal disease				
no	48	23	25	NS
1 location	46	19	27	
>1 location	33	16	17	

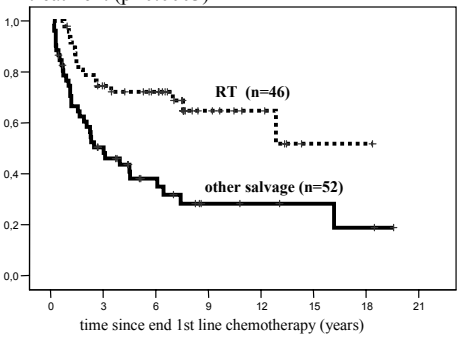
PR=partial response after 8 cycles of doxorubicin based chemotherapy, CR=complete response *Two-sided Fischer's exact

Fig.4

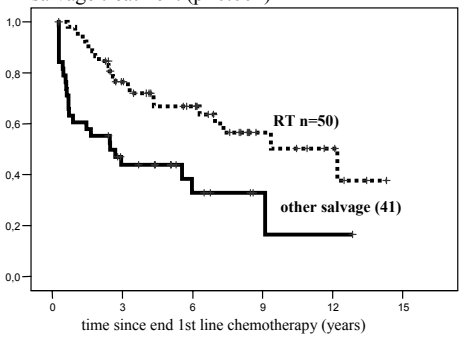
1. Overall survival in PR patients without bulky disease: radiotherapy vs. other salvage treatment (p=0.04)



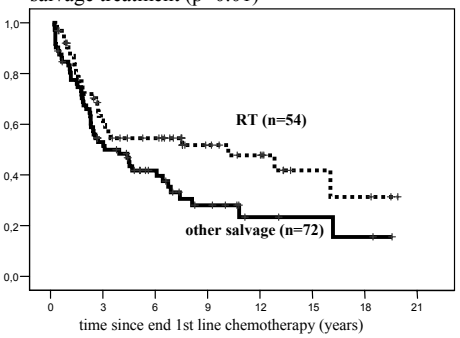
2. Overall survival in PR patients with bulky disease: radiotherapy vs. other salvage treatment (p=0.0003)



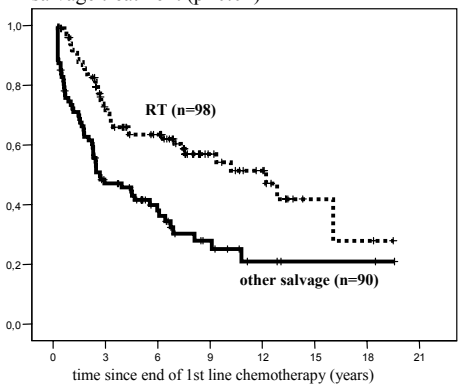
3. Overall survival in PR patients without extranodal disease: radiotherapy vs. other salvage treatment (p=0.002)



4. Overall survival in PR patients with extranodal disease: radiotherapy vs. other salvage treatment (p=0.01)



5. Overall survival in PR patients with an IPI of 2 or less: radiotherapy vs. other salvage treatment (p=0.01)



6. Overall survival in PR patients with an IPI of 3 or more: radiotherapy vs. other salvage treatment (p>0.05)

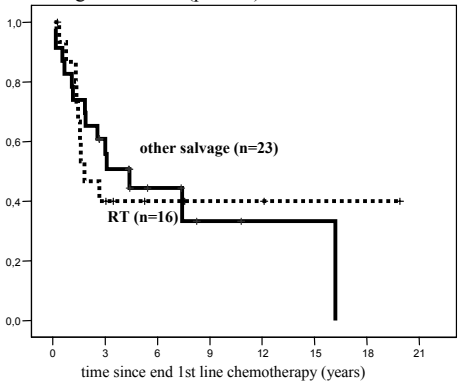
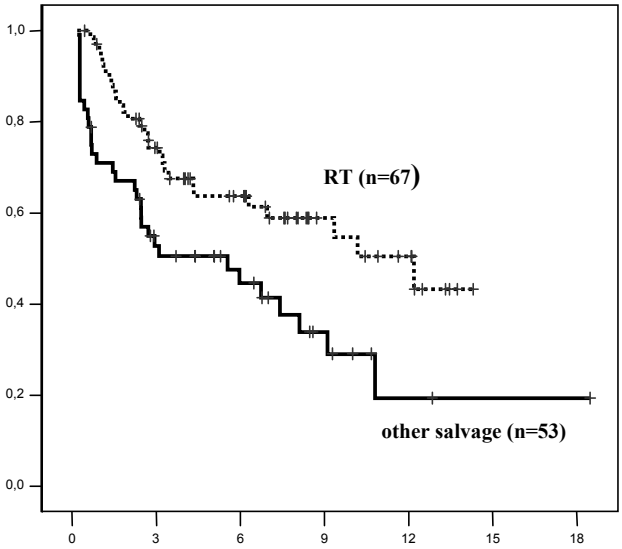


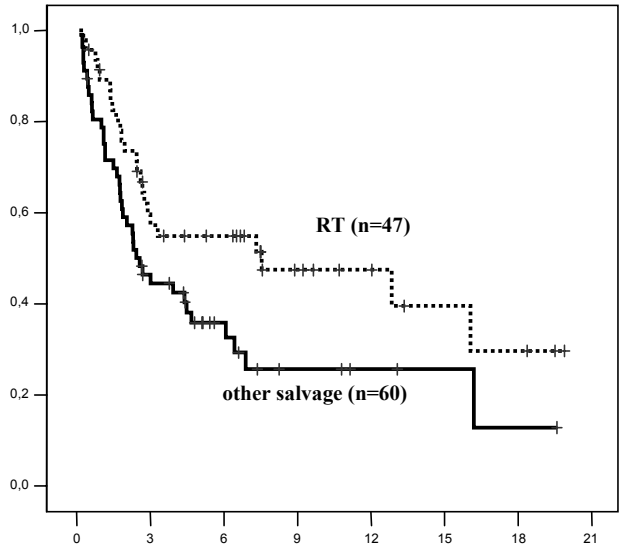
Fig.5 Overall survival comparison in PR patients: radiotherapy vs. other salvage treatment in patients without initial bone marrow involvement (n=120) compared to those with involvement at start of NHL treatment (n=107)

without bone marrow involvement at start :
radiotherapy vs. other salvage (p=0.01)



time since end 1st line chemotherapy

with bone marrow involvement at start :
radiotherapy vs. other salvage (p=0.03)



time since end 1st line chemotherapy

Discussion

In this retrospective analysis on a large EORTC cohort of patients with aggressive NHL, we observed that patients in PR could be durably salvaged by involved field radiotherapy. Radiotherapy could convert a PR to a CR in half of the patients. Survival in patients obtaining a CR by salvage treatment (OS of 57% at 5 years) was comparable to those directly in CR after first line chemotherapy. Patients with a low IPI risk profile benefited most from salvage radiotherapy. The advantage of radiotherapy persisted independently of the presence or absence of unfavorable factors such as extranodal disease, bulky disease or bone marrow involvement at start of first line treatment. The retrospective character of our study hampers the analysis, but selection bias could have influenced the results in both directions. Either the younger and fitter patients in PR could have been considered as better candidates for high dose therapy, or on the other hand the patients with more unfavorable risk factors could have been offered systemic salvage instead of radiotherapy. When patient characteristics in the radiotherapy and other salvage treatment group were compared, factors influencing outcome in both directions were seen as well. Factors favoring a better outcome, such as low IPI and less extranodal NHL involvement were more common in the radiotherapy group. On the other hand, radiotherapy was more frequently given in the older trials, which were found to have an outcome inferior to the more recent trial 20901. As time of treatment, quantified by trial-number, was the most confounding factor introducing selection bias, we stratified all analyses by trial. [21] As the EORTC Lymphoma Group promoted radiotherapy for all patients in PR, not many patients were treated with ASCT. Moreover, our data originate from trials since 1980 and it was only in the beginning of the nineties that ASCT was introduced as salvage treatment. Obviously, we could not compare the outcome after ASCT with RT given the absence of any randomized setting and the low number of patients transplanted. The only point that could be made is that OS en CR conversion rates after radiotherapy or ASCT were superior to second line chemotherapy only. However, our data strongly suggest that PR patients with initial low to intermediate IPI, bulky disease or nodal disease only, can be very well salvaged by involved field radiotherapy, which can be considered a less toxic alternative than ASCT. In patients with higher IPI-risk profiles with bulky disease or nodal disease only, it would be worthwhile to consider the incorporation of involved field radiotherapy to stem-cell salvage as an approach that will integrate both treatment options. Seen the toxicity expected by the combination of treatment, radiotherapy needs to be the first modality given. Despite the fact that radiotherapy has been described as a good salvage option in case of PR in NHL,[10-12] for many groups this is no longer the preferential therapy. Since the successful trial by the Parma group, many consider ASCT as the first choice salvage treatment. [22] It is important to realize that the PARMA-trial was designed for patients in relapse after initial CR to doxorubicin-based chemotherapy, and that only those patients responding to rescue chemotherapy were selected for high dose chemotherapy and autologous bone marrow transplantation. Moreover, (according to the PARMA protocol) half of the patients received radiotherapy before transplant. Obviously, the PARMA-trial was neither designed for patients in PR, nor can the results obtained be extrapolated to this subgroup. The Eastern Cooperative Oncology Group (ECOG) recently published their results of a randomized trial for limited-stage aggressive lymphoma patients. [10] In this trial,

98 (28%) patients obtained a PR and 71 received radiotherapy, after which 22 patients converted to a CR. At 6 years, failure-free survival (63%) and overall survival (69%) were comparable to patients directly in CR. In two other small series of PR patients published by Wilder *et al*[11] and Schlembach *et al*[12], similar results were observed after radiotherapy with better local control and PFS compared to ASCT.

Evidently, the definition of PR – although not changed during the years as far as measurements are concerned – has won in quality by modern imaging techniques. New tools like PET-scans have been introduced to distinguish between remnants of necrotic tissue or viable residual NHL and can therefore differentiate between unconfirmed CR (CRu) and PR. [23, 24] The excellent performance of PET imaging justifies the recent proposal by Cheson *et al* to skip the definition of CRu in the near future. [25] Although in our cohort residual localizations were measured and scored in detail, and in case of doubt cytology or histology had to be performed, PET- or Gallium-scans were not routinely used. By interpreting outcome in old data as ours has to be aware of the fact that the analyzed data originate from trials running from the early 80ies, the period of replacing lymphography by CT-scans, up to more recent years, when more modern techniques as PET- and Gallium imaging were introduced but not yet common practice as they are today. Without doubt, some of these PR's have been unconfirmed CR's according to modern imaging techniques. [26-28] However, as many of our PR patients subsequently relapsed (see Figure 2), and conversion to CR was carefully documented on our measurement forms, we are confident that a large majority of our PR patients would still have fulfilled the present PR criteria. [25-28]
In clinical trials exploring new treatment options, non-CR patients consisting of patients with PR, no change or even progressive disease, are often grouped together as failures. We feel that PR patients should be approached as a separate entity, analyzed separately for prognostic factors predicting response to salvage therapy, and should receive salvage treatment adapted to this PR status. Unfortunately, randomized trials have never been conducted for this subgroup. Obviously, the percentage of patients eligible for such a study will become less, given the better outcome after the introduction of anti-CD20 antibody therapy and the improved quality of response definitions.[3, 23-25] Despite these limitations, we believe that our data, together with those from the ECOG[10] and the MD Anderson group[11, 12] justify a future randomized trial comparing involved field radiotherapy with high dose chemotherapy for - preferably IPI low-risk - patients with a limited (PET-positive) PR.

References

1. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med.328:1002-1006, 1993.
2. Schmitz N, Kloess M, Reiser M, et al: Four versus six courses of a dose-escalated cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen plus etoposide (megaCHOEP) and autologous stem cell transplantation.Cancer 106:136-145, 2006.
3. Coiffier B, Lepage E, Briere J,et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 346:235-242, 2002.
4. Cheson BD, Horning SJ, Coiffier B, et al: Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol

17:1244,1999.
5. Vose JM: High-dose chemotherapy and hematopoietic stem cell transplantation for relapsed or refractory diffuse large-cell non-Hodgkin's lymphoma. Ann Oncol. 9 :S1-3, 1998.
6. Nademanee A, Molina A, Dagis A, et al: Autologous stem-cell transplantation for poor-risk and relapsed intermediate- and high-grade non-Hodgkin's lymphoma. Clin Lymphoma.1: 46-54, 2000.
7. André M, Mounier N, Leleu X et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen. A GELA cohort study on 2837 patients. Blood 103:1222-1228, 2003.
8. Moser EC, Noordijk EM, Carde P, et al: Late non-neoplastic events in patients with aggressive non-Hodgkin's lymphoma in four randomized European Organisation for Research and Treatment of Cancer trials. Clin Lymphoma Myeloma 2:122-130, 2005.
9. Moser EC, Noordijk EM, van Leeuwen FE, et al: Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin's lymphoma. Blood. 107:2912-2919, 2006.
10. Horning SJ, Weller E, Kim K, et al: Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol. 22:3032-3038, 2004.
11. Wilder RB, Rodriguez MA, Tucker SL, et al: Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. Int.J of Rad Oncol Biol Phys 50:743-749, 2001.
12. Schlembach PJ, Wilder RB, Tucker SL, et al: Impact of involved field radiotherapy after CHOP-based chemotherapy on stage III-IV, intermediate grade and large-cell immunoblastic lymphomas. Int J Radiat Oncol Biol Phys 48:1107-1110, 2000.
13. Carde P, Meerwaldt JH, van Glabbeke M, et al: Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non- Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. The EORTC Lymphoma Group. Ann Oncology 2:431-435, 1992.
14. Somers R, Carde P, Thomas J, et al: EORTC study of non-Hodgkin's lymphoma: phase III study comparing CHVmP- VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. Ann Oncology 5 S2:85-89, 1994.
15. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al: Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 93:22-30, 2001.
16. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329: 987-994, 1993.
17. Rosenberg SA, Kaplan HS: Clinical trials in the non-Hodgkin's lymphomata at Stanford University experimental design and preliminary results. Br J Cancer. 31 S2: 456-464, 1975.
18. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457, 1958.
19. Freeman DH. Applied categorical data analysis. Vol.79 of Statistics: Textbooks and monographs. New York, 1987.
20. Cox DR: Regression models and life-tables. J Royal Stat Soc Ser B 334:187-202, 1972.
21. Moser EC, Noordijk EM, van Glabbeke M, et al: Long term efficacy of the CHVmP/BV regimen used for aggressive Non Hodgkin's Lymphoma across three randomized EORTC-trials. Eur J Cancer 40: 474-480, 2004.
22. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 333:1540-1545,1995.
23. Spaepen K, Stroobants S, Verhoef G, Mortelmans L: Positron emission tomography with [(18)F]FDG for therapy response monitoring in lymphoma patients. Eur J Nucl Med Mol Imaging. 30 S1:S97-105, 2003.
24. Filmont JE, Vranjesevic D, Quon A, et al: Conventional imaging and 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography for predicting the clinical outcome of previously treated non-Hodgkin's lymphoma patients. Mol Imaging Biol. 5:232-239, 2003.

25. Cheson BD, Pfistner B, Juweid EM, et al: Revised response criteria for malignant lymphomas from the members of the International Harmonization Project (IHP) of the Competence Network Malignant Lymphoma. Blood (ASH Annual Meeting Abstracts) 106:abstract 18, 2005.
26. Cheson BD: CT/PET scan. Clin Adv Hematol Oncol. 9:483, 2005.
27. Reinhardt MJ, Henkel C, Altehoefer C, et al: Computed tomography and 18F-FDG positron emission tomography for therapy control of Hodgkin's and non-Hodgkin's lymphoma patients: when do we really need FDG-PET? Ann Oncol. 9:1524-1529, 2005.
28. Basaran G, Basaran M, Onat H: Chemoradiotherapy for localized non-Hodgkin's lymphoma: lessons from old studies. J Clin Oncol. 23: 3161-3162; author reply 3162-3163, 2005.

Chapter 4

Late non-neoplastic complications after treatment for aggressive non-Hodgkin's lymphoma across four randomized EORTC-trials

E.C. Moser, E. M. Noordijk, P. Carde, U. Tirelli, J.W. Baars, J. Thomas, D. Bron, J.H. Meerwaldt, M.M.B. van Glabbeke, J.M.M. Raemaekers and J.C. Kluin-Nelemans

Clin Lymphoma Myeloma. 6:122-30,2005.

Abstract

Background: A significant proportion of patients with aggressive non-Hodgkin's lymphoma (NHL) become long-term survivors. An EORTC (European Organisation for Research and Treatment of Cancer) database of patients with aggressive Non Hodgkin's lymphoma (NHL), consistently treated with doxorubicin-based chemotherapy since 1980, afforded the possibility to explore late complications in this patient group.

Patients and methods: Of 951 randomized patients, complete data on late complications could be collected in 757 patients, who were alive for at least 2 years after start therapy and were seen in yearly follow-up (median follow-up 9.4 (2.1-20.4) years). We computed cumulative incidences of late events in a competing risk model by Gray (death being the competing event) to avoid bias caused by the high percentage of NHL-related deaths. Risk factors were estimated in a Cox proportional-hazards model and also evaluated with the Gray-test.

Results: Late non-neoplastic events were observed in 46% of the 757 patients. At 15 years, the cumulative incidences of cardiac disease and infertility were 20% and 29%, respectively. Renal insufficiency (11%), acquired hypertension (8%) and disabling neuropathy (13%) were also frequently observed. Salvage treatment was a risk factor in most events. Smoking and pre-existent hypertension were the main risk factors for cardiovascular disease. In-field radiotherapy was related to hypothyroidism, lung fibrosis, hypertension, gastro-intestinal toxicity and renal insufficiency, but not to cardiovascular events. Autologous stem cell transplantation, cisplatin- and MOPP-containing therapies were associated with infertility and renal insufficiency.

Conclusions: Altogether, almost half of the patients with aggressive NHL experienced events, addressed as late non-neoplastic complications. Salvage therapy, smoking and in-field radiotherapy are important risk factors.

Introduction

Today, a significant proportion of patients with aggressive non-Hodgkin's lymphoma (NHL) become long-term survivors.[1,2] Follow-up in long-term survivors of Hodgkin lymphoma has shown that the cumulative toxicity from treatment can rival the mortality from Hodgkin's lymphoma itself.[3]. In addition to secondary malignancies, delayed effects on the thyroid, reproductive, respiratory, cardiac and gastro-intestinal system were observed.[4, 5]

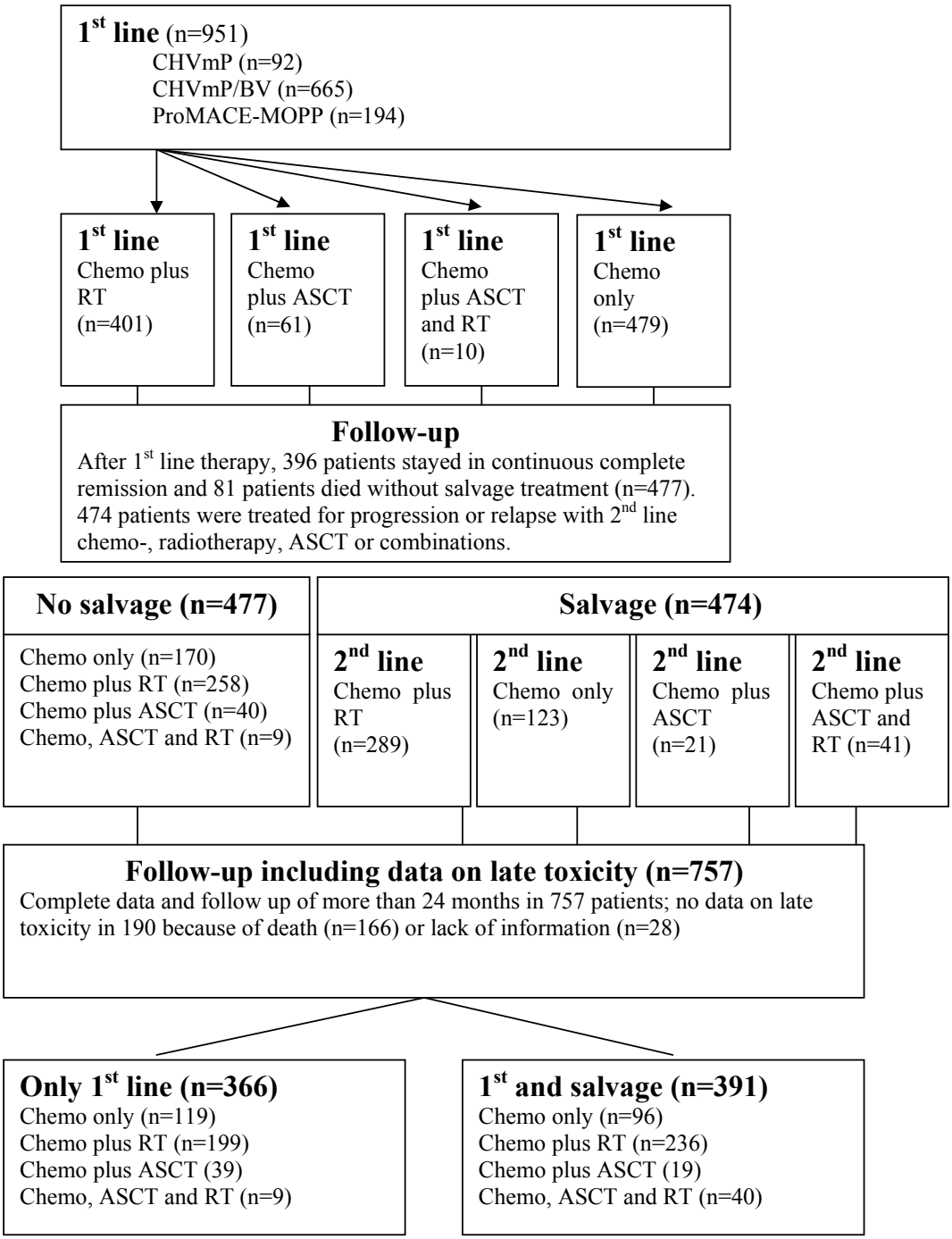
Because patients with NHL are often treated with similar type of drugs and radiotherapy as patients with Hodgkin lymphoma, similar late effects can be expected. However, important differences with Hodgkin lymphoma patients exist: Firstly, NHL patients are older on average and therefore probably more sensitive to vascular damage. Secondly, NHL patients have been increasingly treated with chemotherapy only; during the years, radiotherapy has been given to smaller fields or was not given anymore. Thirdly, because of the higher prevalence of progression and recurrence, salvage treatment is often needed, and by adding more lines of treatment, including autologous stem cell transplantation (ASCT), cumulative toxicity can be expected. Despite the improved overall survival in aggressive NHL, data on late effects are scarce. The complex factors mentioned above probably explain this.

The availability of a large EORTC (European Organization of Research and Treatment of Cancer) database of patients with aggressive NHL, consistently treated with the doxorubicin-based chemotherapy since 1980, offered the possibility to explore late complications in this patient group. Patient records were reviewed and an extra form was filled in by the local physician and checked in the EORTC-Data-center (all patients were kept in yearly follow-up). In this way detailed information on late organ toxicity, smoking habits, pre-existent diseases and salvage therapy were documented. Out of all randomized patients, we selected those who lived at least 2 years after start of treatment and defined late complication as occurring later than 6 months after end of (protocol) treatment.

Herein, we present the data on late toxicity focusing on non-neoplastic adverse events. We correlated these to a series of risk factors, partly defined by patient's characteristics, partly by the therapeutic variability. By doing so, two important caveats in the analyses should be highlighted. Firstly, we could not compare the incidence of non-neoplastic events in the EORTC NHL cohort to incidences in the general population and estimate the relative risk. Our cohort originates from more than five different European countries and registries for the scored non-malignant disorders are lacking in most of Europe. Undoubtedly, due to differences in life-style and genetic profiles, these incidences will differ Europe-wide. Second, estimating the cumulative incidence of late events by the use of Kaplan Meier method[6] would be acceptable for a disease such as Hodgkin lymphoma with few late deaths due to the lymphoma itself, but would give an serious overestimation of late events[7-10] for patients with NHL as many die of their disease before being at risk for any late complication, see also Armitage et al.[11]. To correct for this so-called competing event of (early) death, we estimated incidences of late cardiac, vascular, thyroid, pulmonary, gastro-intestinal, renal, skeletal and neurologic complications by using a competing risk model described by Gray[10] and Gooley[7]. For the estimation of risk factors a multivariate model is needed, but a validated multivariate competing risk model is still lacking. Therefore, we performed multivariate analyses using the Cox proportional-hazards model[12], and analyzed all risk factors with the

Gray-test[10] (competing risk model) as well.

Fig.1. Flow-sheat of NHL treatment



Patients and Methods

Sample Characteristics and Toxicity-related Case Record Forms

Between 1980 and 1999, 951 patients with advanced aggressive NHL patients were treated in four succeeding EORTC-trials (respectively 20802, 20855, 20901 and 20932) (Fig.1). [1, 2, 13-16] All patients were followed yearly until death because of the former trials. The follow-up data consisted of disease status, date and type of relapse (if any), date and cause of death, occurred secondary malignancy or other late toxicity and given treatment. In 2001 all patient records were reviewed, with the help of the local investigators (see appendix A). An extra case record form was filled in; consisting 166 items and covering besides 21 late complications, state of disease, survival and cause of death, also details of treatment after protocol, co-morbidity and smoking habits. Late events were only scored (yes/no/unknown and specification) if considered serious and/or disabling by the local physician, this to reduce the inter-observer variation bias created by the high number of institutes. The local physician documented the date of diagnosis and possible relation with NHL, therapy or pre-existence. Besides doubling of creatinine level for the definition of renal insufficiency, no definitions or laboratory-value limits were given; the diagnosis was left to the local physician. The Protocol Review Committee of the EORTC approved the research protocol and all forms were related and checked in the EORTC Data centre by E. Moser.

Treatment

Most of the patients (75%) received CHVmP/BV as 1st line chemotherapy. This regimen consists of 8 three-weekly cycles of cyclophosphamide, doxorubicin, teniposide, prednisone, with bleomycin and vincristine.[1] In trial 20802,[13, 15] this regimen was compared with CHVmP (without bleomycin and vincristine). In trial 20805,[14] CHVmP/BV was compared to ProMACE-MOPP, consisting of methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine and prednisone. In trial 20901[2] CHVmP/BV was followed by randomization between additional autologous stem cell transplantation (ASCT) or no further treatment; in trial 20932[16] CHVmP/BV was followed by additional radiotherapy or not. Half of the patients needed salvage treatment after 1st line therapy (Fig.1). In the analyses of risk factors we grouped treatment as factor given in both 1st line and/or salvage setting. Radiotherapy given in 1st line or during salvage was documented for dose, fraction, and field. Fields were grouped into regions to relate with the area of the late complication, as specified in Table 1.

Table 1. Patient and treatment characteristics in 757 patients of whom information of late events was collected

Patient and treatment characteristics		**Females (n=295)**	**Males (n=462)**	**Total (n=757)**
Age at start mean (min-max)		48 (16-76)	51 (15-79)	50 (15-79)
Country:	The Netherlands	108	179	287 (38%)
	Belgium	77	108	185 (24%)
	France	51	92	143 (19%)
	Italy	54	75	129 (17%)
	Other	5	8	13 (2%)
Smoking (ever):	Yes	83	222	305 (40%)
	No	197	207	404 (53%)
	Unknown	15	33	48 (7%)
Survival status:	Alive	160	219	379 (50%)
	Dead	135	243	378 (50%)
cause of death :	-NHL	106	184	290 (79%)
	-Toxicity/ Infection	11	17	28 (8%)
	-Cardiovascular disease	9	18	27 (7%)
	-Secondary Malignancy	4	11	15 (4%)
	-other	2	4	6 (2%)
Chemotherapy:				
Bleomycin:	1st line only	182	291	
	salvage	35	52	ever given: 595 (79%)
	both	14	21	never: 162 (21%)
	never	64	98	
MOPP containing:	1st line only	24	33	
	salvage	103	181	
	both	1	0	ever given: 342 (45%)
	never	167	248	never: 415 (55%)
Cisplatin:	salvage without ASCT	12	21	
	salvage with ASCT	19	27	ever given: 79 (10%)
	never	264	414	never: 678 (90%)
ASCT:	1st line only	17	31	
	salvage	20	32	
	both	3	4	ever given: 107 (14%)
	never	255	395	never: 650 (86%)
Radiotherapy:	1st line only	110	162	
	salvage	63	85	
	both	22	42	ever given: 484 (64%)
	never	100	173	never: 273 (36%)
fields given* :	neck	126	192	318 (42%*)
	mediastinum	109	132	241 (32%*)
	hili/lung	35	49	84 (11%*)
	abdomen	109	172	281 (37%*)
	groins	69	93	162 (21%*)
*can be in same patient, % of all 757				

As potential toxic drugs we analyzed bleomycin, cisplatin, and the combination MOPP (containing mechlorethamine and procarbazine). Although CHVmP and ProMACE-MOPP did not contain bleomycin, salvage treatment often did. Cisplatin was only given as part of salvage chemotherapy. The drugs doxorubicin, teniposide, prednisone, vincristine and cyclophosphamide, were not analyzed separately because more than 85% of the patients received these. All 757 patients received doxorubicin; in the CHVmP/BV regimen up to 400 mg/m^2 and in the ProMACE-MOPP-arm up to 200 mg/m^2. The total dose of bleomycin in the 1st line was limited to 80 mg. No cumulative total dose-complication relation was estimated, because dose information of salvage treatment was often lacking. Because all patients did receive doxorubicin-based chemotherapy, we could evaluate the incidence of late effects in this group *and* the additional risk of radiotherapy and drugs (bleomycin, cisplatin and MOPP-containing regimens) when given as well.

Statistical Analysis

The overall survival (date start treatment until date death by any cause) and the progression-free survival (until date progression or death) were calculated by the Kaplan-Meier method.[6] Incidences of late complications were calculated using a cumulative incidence analysis which accounts for competing risk,[7,8,10] with death by any cause as competing event. The time interval was defined as start of initial treatment till date of event or death. Differences in incidence of late events for presence/absence of each separate risk factor were assessed using the Gray-test. Forward and backward multivariate analyses by the Cox proportional hazards model[12] were performed to adjust simultaneously for all potential factors. Results of the two models were compared. In all analyses, we used all and the same variables being: *gender*, *country*, *age* (at start treatment <50 or ≥50 years), *radiotherapy* (in the region of the late effect, as specified in Table 1), *bleomycin-, cisplatin- and MOPP-containing chemotherapy, ASCT* (ever given or not), *smoking* (smoked ever or not), *hypertension* (present before the complication or not). In addition, analyses were done with *salvage* (any second line therapy given or not) as factor between those factors, which were not regarding treatment.

Allocating risk to therapy was performed across trials (non-randomized), resulting in a large sample-size, but risking an imbalance given the differences in time-points as some schemes were more frequently used in the eighties versus ASCT later on. By stratification by trial in all analyses we aimed at correcting the bias created by imbalances and differences in follow-up time among trials, knowing that for the appearance of late complications, time (of follow-up) is the most important factor.

Results

Demography

In 2001, 951 patient records were reviewed. Information on late complications, treatment and survival was collected in 757 patients (Fig.1); 166 patients died within 2 years after start of treatment, and in 28 patients information on late complications was lacking.

All patients had advanced (70% Ann Arbor stage III or IV) and aggressive (82% intermediate grade by Working Formulation[17]) NHL. The median follow-up was 9.4 years (2.4-20.2 years). The overall survival at respectively 5 and 15 years was 58 and 41%, the progression-free

survival 46 and 36%. Half of the patients were still alive at time of the update; the others had died mainly due to recurrence of NHL (79%) or acute toxicity (8%). Nine percent died of non-neoplastic late complications and 4% of secondary cancer (Table 1). Of the 757 patients, 107 received ASCT either as part of 1st line chemotherapy, as salvage-treatment or both. Most ASCT patients received high dose chemotherapy before transplant, mostly consisting of the BEAC or BEAM schemes (BEAC = BCNU, etoposide, cytarabine and cyclophosphamide; BEAM = BCNU, etoposide, cytarabine and melphalan). Five patients received total body irradiation and high dose cyclophosphamide. Two thirds of the patients received radiotherapy at any time during their disease. Patients were irradiated as consolidation for initial bulky disease or slow response, or as salvage therapy. The median dose was 30.4 Gray (20-45 Gray) per treatment, given in fractions of 1.5-2.0 Gray; the cumulative dose never exceeded 50 Gray. When fields are divided in areas, often more regions had been irradiated in the same patient; 42% were irradiated on the neck, 32% on the mediastinum and 37% on the abdomen (Table 1). Of the 241 patients, irradiated on the abdomen; 36 had para-aortic fields (including the both renal arteries and often a small part of the kidney), 86 had fields excluding the kidneys and in 121 patients at least one half of a kidney was in the field.

Incidence of late complications

For fourteen non-neoplastic late complications the overall cumulative incidence was estimated; the rates at 15 years are presented in Table 2. All together, 353 patients (46%) experienced one or more secondary serious non-neoplastic event. On the 757 forms filled in only 9% of the late complications per category was missing or unknown. However, male infertility was scored poor: from 26% of the male patients data were obtained, resulting in only 193 cases to analyze. Male infertility was scored in the whole population (age 15-79 years) and defined by the local physician. Data on female infertility, defined as amenorrhea before the age of 40 years, were scored only in those 62 women (73%) who were younger than 40 at start of treatment.

Information on hypertension - available in 689 patients and present in 43 cases - was evaluated in two ways: as new complication if developed after treatment, and as risk factor if present before the diagnosis of another complication. Other complications, reported but already present before start of treatment, were marked as pre-existent (Table 2), and left out of the analyses.

The rarest complication was avascular bone necrosis (0.5%), whereas the most frequent complications were infertility (up to 29% in women and 18% in men) and cardiac disease, especially myocardial insufficiency (up to 11% at 15 and 22% at 20 years). Most complications became manifest at a median interval of approximately 5 years. Disabling neuropathy occurred early (median 1.1 years), but the incidence still increased over time from 10% at 5 till 14% at 20 years. Of the 59 cases of disabling neuropathy; 6 can be classified as motor and 53 (81%) as sensory neuropathy. In 18 cases the neuropathy was diagnosed as of central origin, whereas of peripheral origin in 41 (68%) patients.

Risk factors for late toxicity

Risk factors linked to patients' characteristics and therapy modalities (absent vs. present)

showed the same impact with both the Gray-test and the Cox proportional-hazards model (Table 3). Sometimes, the impact was not significant in both models, but the trend the same and the numbers small within the sub-set analyses. Salvage treatment in general was the most frequent risk factor (Table 3), related with angina pectoris, myocardial infarction, hypertension, gastro-intestinal toxicity, renal insufficiency, neuropathy and infertility. Radiotherapy on the abdomen was the most important factor for hypertension (Fig.2); without abdominal irradiation this late event was hardly observed. In two thirds of the patients, who received radiotherapy on the abdomen, at least a small part of the kidney was involved, resulting in higher risk of hypertension, but also in renal insufficiency. Radiotherapy, divided in regions treated could be related to hypothyroidism, gastrointestinal toxicity and lung fibrosis as well. On the other hand, in-field radiotherapy did not come out as a risk factor for cardiac disease or large vessel occlusion, whereas age over 50 years during treatment and smoking were in this regard far more important (Fig.2). We separately analyzed all 14 cerebral vascular events, and found also no relation with irradiation of the neck. Lung fibrosis occurred more in younger patients, smokers and after the use of bleomycin. MOPP-containing regimens elevated the incidence of renal insufficiency and male infertility. Cisplatin was related with disabling neuropathy and renal failure.

Table 2 Overview of observed late complications, pre-existent disease and cumulative incidence at 15 years estimated with death of any cause as competing risk.

Late complications observed	**female patients (n=295)**	**male patients (n= 462)**	**Complications vs. pre-existent disease (n=757)**	**% Cumalitive incidence at 15 years**
Cardiac disease (1 or more)	40	63	82 vs. 21	20% (n=697)
-Angina Pectoris or myocardial infarction	13	24	20 vs. 17	5% (n=684)
-Myocardial insufficiency	29	41	70	11% (n=697)
-Rhythm conduction disturbance	13	24	33 vs. 4	6% (n=687)
Large arterial vessel occlusion	19	19	32 vs. 6	7% (n=686)
Hypertension	22	21	18 vs. 25	8% (n=689)
Gastrointestinal ulcers	9	19	28	6% (n=683)
Gastrointestinal perforations	4	5	9	5% (n=683)
Lung fibrosis	14	15	29	6% (n=683)
Renal insufficiency	16	20	36	11% (n=682)
Avascular bone necrosis	1	2	3	0.5% (n=689)
Disabling neuropathy	27	32	59	13% (n=689)
Hypothyroidism	14	9	19 vs. 4	5% (n=652)
Male Infertility		34		18% (n=193)
Female Infertility (in women <40 years)	16			29% (n=62)

Table 3. Analysis of risk factors per complication done within the Cox multivariate model compared to the estimated impact on incidence by Gray-test.

		Cox model		Gray -test	
	significant risk factors	**p-value**	**Hazard Ratio**	**p-value**	**% CI at 15 years (factor absent vs. present)**
Cardiac disease (1 or more)	Age>50 years	0.001	2.2	0.01	13 vs.18%
	Smoking	0.008	1.85	0.03	11 vs. 22%
-Angina Pectoris or myocardial infarction	Hypertension	0.04	3.6	0.01	3 vs. 24%
	Salvage	NS	2.2	0.004	2 vs. 9%
-Myocardial insufficiency	Age>50 years	<0.001	2.7	0.002	6 vs. 15%
	Smoking	0.05	1.5	0.008	7 vs. 14%
-Rhythm disturbance	Hypertension	<0.001	4.7	NS	5 vs.34%
	ASCT	<0.001	4.2	0.02	0 vs. 7%
	Age>50 years	0.03	2.5	0.04	4 vs. 9%
	Smoking	0.03	1.9	NS	5 vs. 10%
Large arterial vessel occlusion	Age>50 years	0.03	2.4	0.003	4 vs. 16%
	Hypertension	0.05	2.5	0.003	5 vs. 19%
Hypertension (new)	RT abdomen	0.002	14.3	0.005	2 vs. 17%
	Age>50 years	0.01	4	0.01	7 vs. 9%
	Smoking	0.03	3	NS	7 vs. 12%
	Salvage	0.03	3.3	NS	5 vs. 11%
Ulcers or perforations	Hypertension	0.01	3.0	NS	5 vs. 18%
	Salvage	0.01	2.5	NS	5 vs. 11%
	RT abdomen	0.05	1.5	NS	6 vs. 11%
Lung fibrosis	Smoking	0.02	2.1	<0.001	2 vs. 5%
	Bleomycin	0.03	4.2	0.05	2 vs. 6%
	RT mediastinum	NS	2.0	0.007	4 vs. 8%
	Age>50 years	NS	0.5	0.02	8 vs. 3%
Renal insufficiency	Salvage	0.02	5.2	<0.001	2 vs. 9%
	Hypertension	0.03	3.4	NS	5 vs. 8%
	Cisplatin	0.05	2.4	NS	4 vs. 13%
	ASCT	NS	1.6	0.01	4 vs. 8%
	RT abdomen	NS	1.5	0.02	5 vs. 8%
	MOPP-containing	NS	1.5	0.02	5 vs. 9%
Disabling neuropathy	Salvage	0.007	2.5	NS	10 vs. 15%
	Cisplatin	NS	1.7	0.05	12 vs. 23%
Hypothyroidism	RT neck	0.05	2.4	0.04	4 vs. 6%
	Gender M/F	0.05	2.1	0.05	4 vs. 7%
Male Infertility (n=193)	MOPP-containing	0.03	3.0	NS	11 vs.21%
	ASCT	NS	2.4	NS	12 vs. 20%
	Cisplatin	NS	1.4	0.03	11 vs. 24%
Female Infertility (n=58)	ASCT	0.01	3.2	NS	23 vs. 75%
	Salvage	0.04	2.6	NS	23 vs. 29%
	RT abdomen	NS	1.5	NS	26 vs. 31%
	MOPP-containing	NS	1.4	NS	24 vs. 28%
	Cisplatin	NS	1.4	NS	19 vs. 25%

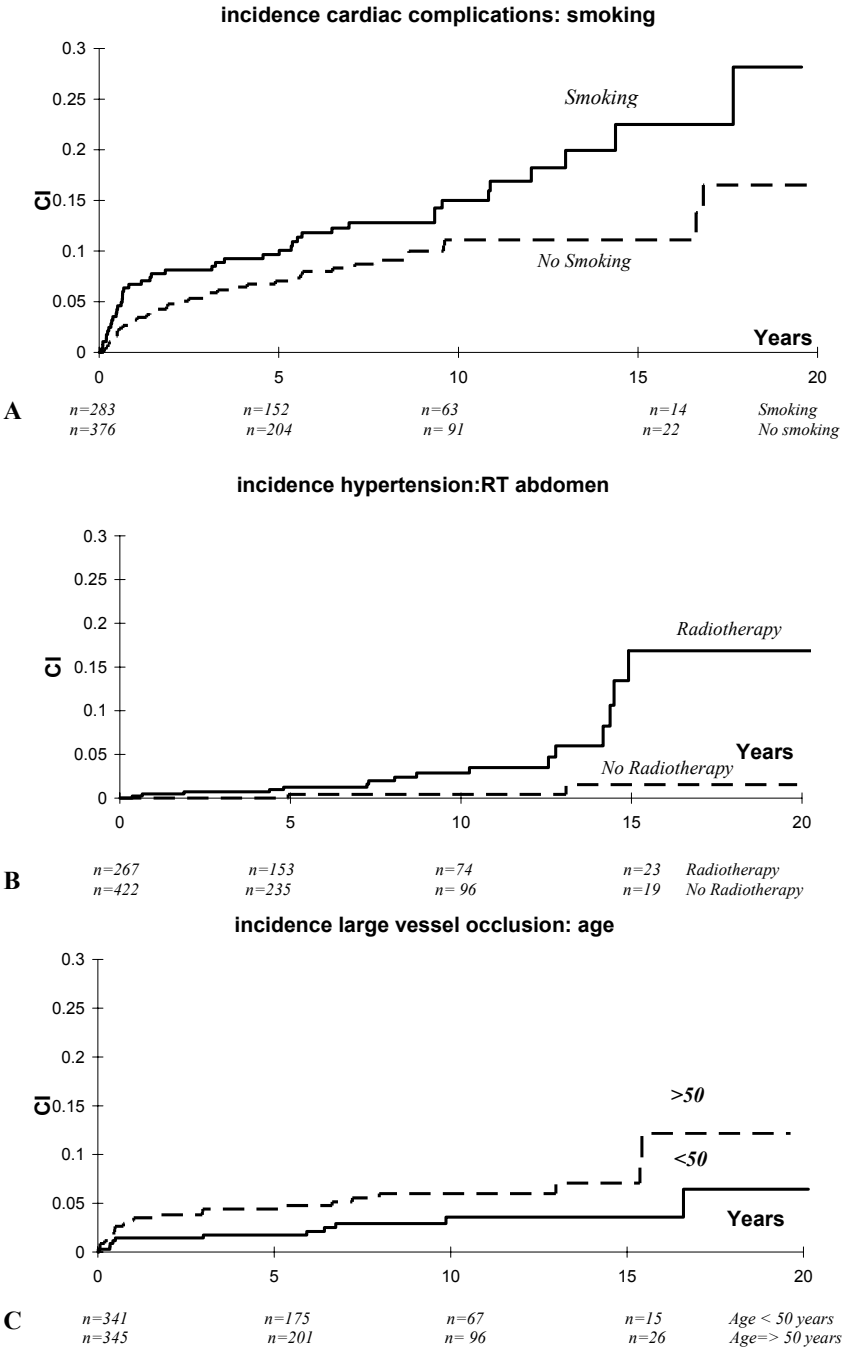
ASCT was associated with a higher risk of renal insufficiency, but also with cardiac rhythm disturbances. This last event was only observed in patients who had received ASCT and not in those salvaged in any other way (0 vs. 7% at 15 years).

Discussion

This is one of the first studies showing in great detail that late non-neoplastic toxicity occurs frequently after curative therapy for aggressive NHL. Half of the patients experienced one or more secondary serious non-neoplastic event, out of which probably a majority can be considered as late complications seriously hampering quality of life, and even having contributed to early death. The study required consultation of the original patient records covering a time-period of twenty years and resulted in an exceptional high response rate of almost 90%. Our investigation unravelled not only a variety of complications but also the complexity of (salvage) treatment in NHL patients. Evidently, the retrospective design of this analysis caused serious restrictions. A prospective analysis on non-malignant toxicity would have offered the possibility to collect in a much more detailed way, information on the development of new diseases and potential risk factors. For example, smoking habits could then have analyzed in more detail (not just ever or never smoked, but pack-years, years of exposure, any exposure during therapy) and in the case of hypertension one would have liked to know the duration, grade, and if anti-hypertensive treatment was given. However, such prospective trials have not been performed, and will hardly be feasible given the enormous amount of extra workload for data collection. Even for Hodgkin Lymphoma trials, where physicians and patients are much more aware of the importance of monitoring late (non-malignant) toxicity, the compliance to collect additional data is generally very low. Therefore, we choose for the second-best option: a retrospective analysis on an initially uniformly treated cohort of patients with aggressive NHL, using a specifically designed case record form. To guarantee good compliance, we restricted ourselves to 21 different late complications (neoplastic and non-neoplastic), and left it up to the physician to decide whether the co-morbidity mentioned was serious or disabling, knowing that it would be impossible to go into more detail, or to verify this item in a cohort of patients of whom many subsequently had died. Nevertheless, with all these restrictions in mind, we feel that we collected important data. Our aim was to present a general picture of the patient with aggressive NHL treated with CHOP and (on indication) involved-field radiotherapy with the late complications encountered in this group. Our risk factor analyses can help the physician to address risk on a more individual base, taking additional factors as smoking, salvage etc into account. Although some data on late toxicity after NHL therapy have been published, these concerned only small groups of patients[18] or focused on a restricted number of items already present in the databases.[19-23] In the EORTC cohort, detailed information on the radiotherapy (in-field), given to more than half of the patients, was collected. Throughout the years, radiotherapy was given according to protocol as involved-field treatment without important variations. No extended fields or old techniques as contact- or Cobalt-treatments were given. Doses and fields were prescribed and blocks, where needed, advised. We observed many late events related to radiotherapy. We could confirm late organ toxicity already observed in other malignancies treated with radiotherapy, such as hypothyroidism,[20]

lung fibrosis,[21] hypertension, renal insufficiency[22,23] and gastrointestinal toxicity.[24] On the other hand, we found no relation between cardiac- and vascular events and radiotherapy as often suggested.[8, 19, 25-27]

Fig.2. Cumulative incidence (CI) of cardiovascular complications and hypertension over time related to smoking habits (A), in-field radiotherapy (B) and age (C).



The common policy during the last decades using restricted radiotherapy on the mediastinum with shielding of the heart might explain these findings. In our NHL cohort of patients with a median age of 50 years at start of therapy, cardiovascular toxicity was clearly more related to smoking and hypertension than to therapy-related factors. This supports the data from Eifel et al[28] that advising a healthier life-style is as important as aiming at lower doses of radio- and chemotherapy. Evidently, for a true estimate of the potential increase (relative risk) of late events, incidence rates in the general population are needed, such as exist for cancer.[29,30] Therefore, we could not compare the NHL patients with the normal population. Instead, we evaluated risk factors *within* patient-groups. By doing so, we came upon remarkable findings, such as the strong relationship between radiotherapy on the abdomen and hypertension that became manifest only after an interval of 10 years after initial therapy. Although hypertension is a typical event related to age, it was clear from our data, that radiotherapy was a much stronger contributing risk factor. Moreover, it became also obvious that long-term follow-up is required to observe such an event. In relating chemotherapeutic agents to late toxicity, we faced the problem of the complexity in salvage regimens. Most drugs were given both in 1st line and as salvage treatment. Out of series of diverse (rescue) regimens, we selected potential toxic drugs, given besides doxorubicin. After making a general comparison with salvage as additional factor, we compared those drugs, given extra in enough but not in all patients, so that we could make a significant comparison between given or not. In this way we estimated the additional risk of in-field radiotherapy, transplant regimens (which consisted in 95% of BEAM or BEAC chemotherapy), MOPP consisting regimens, bleomycin and cisplatin. The fact that salvage therapy was a risk factor for almost all complications was also apparent in the GELA analysis[19], underlining that cumulative toxicity is an important cause of late toxicity in patients with poor progression-free survival. This dose-relation is probably also the reason for the frequently found late neuropathy. Postma *et al*[31] studied neuropathy in 40 NHL patients, treated by CHOP chemotherapy and observed temporary abnormalities in more than half of them (median follow-up of 34 months). In contrast, in our study with longer follow-up, the neuropathy appeared to increase even further over time. Similarly to the patients studied by Postma *et al,*[31] all our patients had received vincristin. We analyzed as obvious additional risk factor the use of cisplatin, which was applied in salvage regimens. Cisplatin did indeed increase late neuropathy rates, but also without cisplatin patients suffered from this complication. As expected from other malignancies, bleomycin[32] and radiotherapy[21] were risk factors for lung fibrosis, but here also smoking and age played an important role. MOPP-containing regimens and high dose chemotherapy before ASCT are known to induce male infertility,[33-36] in our study infertility was also seen in patients treated with doxorubin-based chemotherapy alone. For addressing risk in combined modality treatment, suitable and validated statistical models are needed instead of comparing (crude) incidences between groups with single modality treatment. Duration of follow-up in this is crucial, given the increasing incidence over time of all late complications. A short follow-up for chemotherapy gives an underestimation of risk when compared to an "older" treatment as radiotherapy. The methods, by which the incidence rates and risks are analyzed, have major impact on the results. In patient groups with poor (progression-free) survival, correcting for death is strongly recommended by using a competing risk model. In our analyses the Cox

model helped in unraveling potential risk factors for late toxicity *and* death, supplementary to the Gray-test. Development of practical multivariate competing risk models will improve studies like ours in the future.

In conclusion, half of the long-term survivors of aggressive NHL encounter one of more serious non-neoplastic late complication. If these events can be addressed as complication of treatment in all cases has to be seen; factors as age, smoking and hypertension play clearly their role as well. This incidence of events in our cohort is higher than found in the GELA-cohort[19], and reflects the importance of long-term follow-up. Continuing surveillance to anticipate and prevent late complications is advised for NHL survivors like those of Hodgkin Lymphoma. Salvage therapy, age over 50 years, smoking and hypertension largely increase the risk of late complications. In addition, patients irradiated on neck, mediastinum and abdomen need monitoring of thyroid, pulmonary, blood pressure and renal function. Treatment with ASCT or cisplatin- and MOPP-containing regimens endangers fertility and renal function, on which can be anticipated. Moreover, control of hypertension and quitting smoking can preserve a better quality and longer life for those who survive an aggressive NHL.

References

1. Moser EC, Noordijk EM, van Glabbeke M, et al. Long term efficacy of the CHVmP/BV regimen used for aggressive Non Hodgkin's Lymphoma across three randomized EORTC-trials. Eur J Cancer 2004;40:474-80.
2. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst 2001;93:22-30.
3. Hancock SL, Hoppe RT. Long-term complications of treatment and causes of mortality after Hodgkin's disease. Semin Radiat Oncol 1996;6:225-242.
4. Hoppe RT. Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol 8 Suppl 1997;1:115-8.
5. Armitage JO. Long-term toxicity of the treatment of Hodgkin's disease. Ann Oncol 1998;9 Suppl 5:S133-6.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457.
7. Gooley TA, Leisenring W, Crowley J,et al. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695-706.
8. Pepe MS, Mori M. Kaplan Meier marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med 1993;12:737.
9. Kalbfleisch JD, Prentice RL. Statistical Analysis of Failure Time Data. New York, USA: Wiley, 1980;163-78.
10. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statistics 1988;16:1141-54.
11. Armitage JO, Carbone PP, Connors JM, et al. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21(5):897-906.
12. Cox DR. Regression models and life-tables. J Royal Stat Soc Ser B 1972;334:187-202.
13. Carde P, Meerwaldt JH, van Glabbeke M, et al. Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non- Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. The EORTC Lymphoma Group. Ann Oncology 1992;2:431-5.
14. Somers R, Carde P,Thomas J, et al. EORTC study of non-Hodgkin's lymphoma: phase III study comparing

CHVmP- VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. Ann Oncology 1994;5 Suppl 2:85-9.
15. Meerwaldt JH, Carde P, Somers R, et al. Persistent improved results after adding vincristine and bleomycin to a cyclophosphamide/hydroxorubicin/Vm-26/prednisone combination (CHVmP) in stage III-IV intermediate- and high-grade non-Hodgkin's lymphoma. The EORTC Lymphoma Cooperative Group. Ann Oncology 1997;8 Suppl 1:67-70.
16. Raemaekers J, Kluin-Nelemans H, Teodorovic I, et al. The achievements of the EORTC Lymphoma Group. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002;38 Suppl 4:S107-13.
17. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997;89:3909-18.
18. Haddy TB, Adde MA, McCalla J, et al. Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol 1998;16:2070-9.
19. André M, Mounier N, Leleu X et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen. A GELA cohort study on 2837 patients. Blood 2003;15;103:1222-8.
20. Peerboom PF, Hassink EAM, Melkert R. Thyroid function 10-18 years after mantle field irradiation for Hodgkin's disease. Eur J Cancer 1992;28A:1716-18.
21. Dubray B, Henry-Amar M, Meerwaldt JH, et al. Radiation-induced lung damage after thoracic irradiation for Hodgkin's disease: the role of fractionation. Radiother Oncol 1995;36:211-7.
22. Fels LM, Bokemeyer C, van Rhee J, et al. Evaluation of late nephrotoxicity in long-term survivors of Hodgkin's disease. Oncology 1996;53:73-8.
23. Irwin C, Fyles A, Wong CS, Cheung CM, Zhu Y. Late renal function following whole abdominal rradiation. Rad Oncol 1996;38:257-61.
24. Cosset JM, Henry-Amar M, Burgers JM, et al. Late radiation injuries of the gastrointestinal tract in the H2 and H5 EORTC Hodgkin's disease trials: emphasis on the role of exploratory laparotomy and fractionation. Radiother Oncol 1988;13:61-8.
25. Heikens J, Ubbink MC, van der Pal HP. Long-term survivors of childhood brain cancer have an increased risk for cardiovascular disease. Cancer 2000;88:2116-21.
26. Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors. Cancer 2003;97:663-70.
27. Stewart JR, Fajardo LF, Gilette SM, Constine LS. Radiation injury to the heart. Int J Radiat Oncol Biol Phys 1995;31:1205-11.
28. Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol 2002;20:3651-3657.
29. Van der Sanden GAC, Coebergh JWW, Schouten LJ, Visser O, Van Leeuwen FE. Cancer incidence in the Netherlands in 1989 and 1990: first results of the nationwide Netherlands Cancer Registry. 1995;31A:1822-28.
30. Ries LAG, Eisner MP, Kosary CL. SEER cancer statistics review 1973-1997. Bethesda, USA: National Cancer Institute, 2000.
31. Postma TJ, Benard BA, Huijgens PC, Ossenkoppele GJ, Heimans JJ. Long-term effects of vincristine on the peripheral nervous system. J Neurol Oncol 1993;15:23-7.
32. Comis RL. Bleomycin pulmonary toxicity: current status and future directions. Semin Oncol 1992;19:64-70.
33. Franchi-Rezgui P, Rousselot P, Espié M, et al. Fertility in young women after chemotherapy with alkylating agents for Hodgkin and non Hodgkin lymphomas. Haematology 2003;4:116-20.
34. Bokemeyer C, Schmoll HJ, van Rhee J, Kuczyk M, Schuppert F, Poliwoda H. Long-term gonadal toxicity after therapy for Hodgkin's and non- Hodgkin's lymphoma. Ann Hematol 1994;68:105-10.
35. Naccache P, Decaudin D, Koscielny S, Bendahmane B, Auger J, Munck JN. Semen preservation and gonadal toxicity in the treatment of non Hodgkin lymphoma. Experience at the Gustave-Roussy Institute

from 1980 to 1993. Bull Cancer 1996;83:307-14.
36. Krieger G, Kreysing E, Kneba M: Long-term results with MACOP-B and radiation therapy for aggressive lymphomas. Onkologie 2001;24 Suppl 1:49-58.

Chapter 5

Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin's lymphoma.

E.C. Moser, F.E. van Leeuwen, E.M. Noordijk, S. le Sessie, J.W. Baars, J. Thomas, P. Carde, J.H. Meerwaldt, M.M.B. van Glabbeke and J.C. Kluin-Nelemans

Blood 107: 2912-19, 2006.

Abstract

Cardiovascular disease frequently occurs after lymphoma therapy, but is common in the general population too. Therefore, risk estimation requires comparison to population-based rates. We calculated risk by standardized incidence ratios (SIRs) and absolute excess risks (AERs) per 10,000 person-years based on general population rates (Continuous Morbidity Registry Nijmegen) in 476 (Dutch and Belgian) patients with aggressive non Hodgkin's lymphoma (NHL) treated with at least 6 cycles of doxorubicin-based chemotherapy in 4 EORTC trials (1980-1999). Cumulative incidence of cardiovascular disease, estimated in a competing risk model was 12% at 5 years and 22% at 10 years (median follow-up 8.4 years). Risk for chronic heart failure appeared markedly increased (SIR 5.4, 95% CI 4.1-6.9) with an AER of 208 excess cases per 10,000 py, whereas risk of coronary artery disease matched the general population (SIR 1.2, 95% CI; 0.8-1.8, AER 8/10,000 py). Risk of stroke was raised (SIR 1.8, 95% CI; 1.1-2.4, AER 15/10,000 py), especially after additional radiotherapy (more than 40Gy). Pre-existent hypertension, NHL at young age and salvage treatment increased risk for all cardiovascular events; the impact of radiotherapy was dose-dependent.

In conclusion, patients are at long-term high risk of chronic heart failure after NHL treatment and need therefore life-long monitoring. In contrast, risk of coronary artery disease appeared more age-dependent than treatment related.

Introduction

Nowadays, many patients with malignant lymphoma become long-term survivors. During follow-up, therapy-related late sequelae have become an important issue. Whereas secondary cancers were the first to be noticed,[1-3] non-malignant late sequelae, especially related to cardiovascular disease, are considered important as well.[3-8] Most reports on cardiovascular disease in long-term follow-up of patients with malignant lymphoma concern patients with Hodgkin's lymphoma mainly treated with radiotherapy.[7-12] Patients with aggressive non-Hodgkin's lymphoma (NHL) are generally older than HL patients and are because of age alone, already at risk for cardiovascular disease. The large majority of these patients will receive doxorubicin-based chemotherapy with cumulative doxorubicin doses up to 300-400 mg/m^2.[13] Moreover, as about half of the patients will not obtain a complete response, and another large percentage will relapse afterwards, salvage treatment is often needed. Involved field radiotherapy and autologous stem cell transplantation (ASCT) have been introduced to improve survival but can also become contributing factors to eventual late sequelae.[14-18]

The availability of a large EORTC (European Organization of Research and Treatment of Cancer) database of patients with aggressive NHL, consistently treated with doxorubicin-based chemotherapy, offered the possibility to explore risk of cardiovascular disease in long-term follow-up. Detailed information on additional treatment was collected to evaluate excess risk due to multi- modality treatment.

Cardiovascular toxicity, which has mainly been studied in breast cancer and HL patients, is described to be dose, gender and age dependent.[19, 20] In the general population, the incidence of cardiovascular disease is similarly related to age and gender.[21, 22] Other factors influencing risk of cardiovascular disease, i.e. hypertension, socio-economic status, life-style (diet and smoking), familiar predisposition, but also medical care (prevention and intervention) may vary geographically and over time.[23-26] Therefore, risk estimation requires comparison to population-based rates. We compared the incidence of cardiovascular disease in our EORTC cohort to general population rates using a large Dutch population-based morbidity registry.

Patients and Methods

Data collection procedures

A retrospective cohort study was performed in 974 patients with advanced aggressive NHL enrolled in 4 successive EORTC trials between 1980 and 1999. To relate risk to the general (Dutch) population, we selected patients treated in the Netherlands or Belgium (incidence rates in Belgium were supposed to be comparable to those registered in the Netherlands).[25-27] Patient records were reviewed by the local investigators (see appendix A), and the following data were collected: sex, age, International Prognostic Index (IPI),[28] smoking habits, pre-existing hypertension, date of start of chemotherapy, specification of regimen (1st line and salvage treatment), additional ASCT and/or radiotherapy (including field, dose and timing), date of death, cause of death, date of last follow-up, date of diagnosis of secondary event, cause and specification of cardiovascular disease. No routine electrocardiograph (ECG) or other tests had been performed to detect subclinical cardio-toxicity during follow-up, only clinical diagnoses and the most plausible cause of cardiovascular disease were registered. Unfortunately, no sufficient data on other risk factors such as familiar predisposition, obesity,

hypercholesterolemia, hypertriglyceridemia or diabetes mellitus were available. For details related to the specifically designed case record forms, see Moser et al. [6]
We restricted the analyses to those patients treated with at least 6 cycles of doxorubicin-based chemotherapy and with a minimal follow-up time of 0.5 year. Patients with a history of cardiovascular disease were excluded, except patients with pre-existent hypertension.

General population rates
In this study, we used data derived from the Continuous Morbidity Registration of the Department of General Practice (GP) at the University of Nijmegen (CMRN).[29, 30] In this database every episode of morbidity presented to the GPs in four affiliated practices has been registered since 1971. Comparison of recent incidence rates of cardiovascular disease from the CMRN with those of several new registries in the Netherlands, comprising short-term incidence rates, showed that incidence rates of CMRN were similar to the mean of all registries combined, indicating that the CMRN is representative of the Netherlands. [31]
The relevance and limitations of this database are directly influenced by the Dutch health care system: nearly all residents have a GP and not only those seeking medical care. GPs receive all medical correspondence from attending physicians regarding their patients. Every GP has a stable practice population, being the official person to access specialized medical care. Hence, the dataset consists of the entire primary health care provided to the population as well as referrals for health care. The outcome of interest of the CMRN is estimating incidence of the most common diseases in the general population, according to age and gender over time. The diagnoses are registered in a primarily disease-oriented classification based on the International Classification of Health Problems in Primary Care (ICHPPC-2). We selected 5 diagnoses: first myocardial infarction, first attack of angina pectoris, chronic heart failure (also named congestive heart failure), coronary artery disease and cerebrovascular accidents.

Definitions
According to the definitions used in the CMRN database, we used diagnoses based on the ICHPPC-2. Incidence rates in our cohort and those registered by the CMRN both allowed multiple separate diagnoses per person, but only the first of the given diagnosis was recorded.
Chronic heart failure was defined as clinical congestive heart failure class II or more by the New York Heart Association criteria (NYHA) meaning that although the patient could be comfortable at rest, ordinary physical activity caused symptoms. Coronary artery disease including angina pectoris or myocardial infarctions were also registered if at least class II NYHA. For angina pectoris, one of the following criteria has to be met: pre-cordial chest pain characteristic for angina pectoris, ischemia on the ECG, or confirmed sclerosis on the angiography. For myocardial infarction, the criteria are pre-cordial pain typical for myocardial infarction longer than 15 minutes and one of the following: abnormal ST-T segments or Q waves on the ECG; raised serum levels of enzymes. Vascular disease was registered as large vessel occlusion causing pain and/or loss of physical function, needing (urgent) intervention and hospital admission. No distinction was made in outcome: both lethal and non-lethal

cardiovascular events were included. Smoking was scored positively when the patient had ever smoked, also when (s)he quitted during follow-up. Hypertension was scored as present if medically treated and diagnosed before the cardiovascular event.

Treatment

All patients had received at least 6 cycles of chemotherapy containing doxorubicin; up to 400 mg/m^2 in the CHVmP/BV regimen given in all 4 trials (consisting of cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin and vincristine) and CHVmP (CHVmP/BV without bleomycin and vincristin) in the first trial; and up to 200 mg/m^2 with the ProMACE-MOPP regimen (consisting of doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, procarbazine, methotrexate and prednisone) in the second trial.[32-35] No cumulative total dose doxorubicin-complication relation could be estimated, because dose information of salvage treatment was often lacking.

To relate cardiovascular events to involved field radiotherapy, all fields were retrospectively checked and the cumulative dose per field (specified as mediastinum, neck, abdomen or groin) was estimated. The advised dose in all EORTC protocols was 30 Gy for patients with initially bulky disease (>5 cm) in complete response after first line chemotherapy, and 40 Gy for partial response (in fractions of 1.5-2 Gy). If large fields were needed, a reduction of the field, focusing on the remaining lesion was suggested for the last 4-10 Gy. For extranodal locations dose was limited to 20-30 Gy with a boost of 4-10 Gy after field reduction. In the salvage setting, often the same dose-levels were used.

Statistical Analysis

A comparison was made between the incidence of cardiovascular disease in the study population and the incidence in the Dutch population (CMRN database). In this person-years type of analysis, the ratio of observed and expected number of cardiovascular events was determined. The observed/expected ratio will further be denoted as the Standard Incidence Ratio (SIR). Expected numbers were computed with the use of age-, sex-, and calendar period-specific incidence rates derived from the CMRN database. Absolute excess risk (AER per 10,000 person-years) was calculated as the observed number of cardiovascular events in our cohort minus the number expected, divided by number of person-years at risk, multiplied by 10,000. AER expresses the excess cases per 10,000 person-years diagnosed in the study group compared to the general population and is seen as the best way to asses the burden of treatment sequelae in a patient population. The incidences per person-year were categorized by age in 5 years-intervals (running from 15 to 85 years), by sex and by calendar period in 2 to 3 years-intervals (running from 1980 to 2001) in both the study and the CMRN cohort. CMRN incidence rates for coronary artery disease were available from 1971 to 2000 (3 year moving averages), but for stroke and chronic heart failure only from 1985 to the end of 2000. Therefore, the person-time analysis for chronic heart failure and stroke was started at January 1, 1985, and for coronary artery disease at January 5, 1980 (first patient enrolled). In all patients accumulation of person-time at risk for cardiovascular disease began at 0.5 years after start of NHL treatment and ended at date of diagnosis of the event, date of death, or most recent information on cardiovascular disease occurrence, whichever came first. When

analyzing *one* specific cardiovascular diagnosis, observed numbers were based on all *first* events of this given diagnosis occurring at least 0.5 year after start NHL treatment in the study cohort, since the expected numbers of events were recorded correspondingly in the CMRN cohort. The case record forms offered coronary artery disease, myocardial infarction and angina pectoris as separate items to fill in, which explains why all three are overlapping (see Table 2). In the analyses of coronary artery disease, time at risk ended at the day of diagnosis of one of the three events. Confidence limits were calculated using exact Poisson probabilities of observed numbers. [36] To assess treatment effects on risk of cardiovascular disease among other possible factors, we distinguished different subgroups: patients younger vs. older than 55 years at start of treatment, those with vs. without pre-existing hypertension, who had vs. who had never smoked, who received vs. did not need (any) salvage treatment, who received additional ASCT in the first line or as salvage treatment vs. did never receive ASCT and who were additional irradiated on the neck or heart region (depending on the event) in the first line or as salvage treatment vs. did never receive radiotherapy in this region. We repeated the overall and subgroup analyses in those patients with at least 3 (n=305) and 5 years (n=240) of follow-up and in those patients treated (and often cured by) only in the first line (n=253). Median follow-up, time to occurrence and survival were estimated as a function of time since start of NHL treatment and analyzed according to the product-limit method first described by Kaplan and Meier, censoring for death, lost to follow-up and event (whatever came first).[37] Cumulative incidences of cardiovascular disease were estimated in the competing risk model by Gray with death by any cause as competing event.[38] The Cox proportional-hazards model [39] was used to quantify the effects of different treatments on risk *within* the patient group, adjusting for confounders, as opposed to the person-years analysis in which risk is compared with the general population. Forward stepwise confounder selection, in which the effect of adding one confounder at the time was evaluated, was based on a more than 10% change in the risk estimate of the exposure variable of interest, irrespective of significant values. Variables evaluated in this model were age at start of treatment, trial (since the 4 trials were successively performed, this reflects also the calendar period of treatment), IPI, smoking, pre-existent hypertension, additional salvage (any type), ASCT and radiotherapy (in region of event). Age was analyzed as continuous variable; other factors were categorized (yes vs. no). Cox's models were fitted using SPSS statistical software (SPSS, Inc Chicago, IL).

Results

Within the 4 EORTC trials for advanced aggressive NHL, 592 patients (61%) had been treated in the Netherlands or Belgium between 1980 and 1999. Seventy-one had a follow-up of less than 0.5 year due to early progression or death, and 9 patients had a history of cardiovascular disease. In 476 of the remaining 512 cases follow-up information on survival, treatment and cardiovascular risk was complete until death or January 1st, 2001. The quality of the forms was excellent with only 7% missing data, spread over the various items. The characteristics of the 476 patients according to the selected subgroups are described in Table 1. There were more men than women. The mean age was 49, ranging from 16 to 82 years. Most patients had stage III or IV disease (68%) and 45% had a low-intermediate, 34% an intermediate-high and 21% a high IPI risk profile.

Half of the patients (51%) received any salvage regimen. Of the 235 patients cured in the first line, 170 received only doxorubicin-based chemotherapy, 25 chemotherapy followed by ASCT, and the remaining received chemotherapy with radiotherapy on the neck (n=66) and/or on the mediastinum (n=52). If all patients were taken into account, 139 patients received radiotherapy on the mediastinum and 189 on the neck. Fifty-six patients received an ASCT of whom 31 as salvage. The median radiotherapy dose on the neck was 36 Gy (range 28-60 Gy), the mediastinum 32 Gy (range 28-56 Gy), abdominal fields 36 Gy (range 20-42 Gy) and the groins 38 Gy (range 28-50 Gy). Sixty-one patients were irradiated more than once in the same area: 38 on the same side of the neck, 18 on the mediastinum, and 10 with a field containing the same groin and 5 in the same abdominal region. ASCT was preceded by high dose chemotherapy; no total body irradiation had been given.

The median follow-up was 8.4 years, the median survival 8.6 years (range 0.8-20.5). Overall survival at 5 and 10 years was 65% and 36% respectively. Progression-free survival at 5 and 10 years was 45% and 32%, respectively. The most common cause of death was NHL (90%), whereas 7% of the patients died of cardiovascular disease.

Table 2 shows the number of observed and expected cardiovascular events, number of patients, overall SIRs with 95% confidence limits and AERs per 10,000 person years. Because population-rates for chronic heart failure and stroke were only available from 1985, these analyses were restricted to the 441 patients still alive and without cardiovascular disease from this point in time. A total of 66 new cases of chronic heart failure were observed after NHL treatment, 64 after 1985, compared to 12 expected on the basis of general population rates (SIR 5.4, 95% CI; 4.1-6.9). Risk for chronic heart failure was markedly increased; the AER amounted to 208 excess cases per 10,000 person-years. On the other hand, incidence of coronary artery disease was not significantly different in the NHL patients compared to the Dutch population. Seventeen first myocardial infarctions were reported, while 14.8 were expected: resulting in SIR of 1.2 (95% CI; 0.8-2.4) and an AER of 8/10,000 person-years. As cause of chronic heart failure, coronary artery disease was reported in 20 cases (30%), cardiomyopathy in 14 (21%) and valvular disease in four (6%). In 28 cases (42%) chronic heart failure was accompanied by rhythm disturbances.

Table 1. Patient characteristics at start of first line NHL treatment

	Men (n=292)	Women (n=184)	Total (n=476)
Age			
younger than 55 years	178	116	294 (62%)
55 or older	114	68	182 (38%)
Ann Arbor Stage			
I bulky	11	7	18 (3%)
II	85	53	138 (29%)
III	79	43	122 (26%)
IV	117	81	198 (42%)
International Prognostic Index			
low-intermediate	136	76	212 (45%)
intermediate	98	63	161 (34%)
intermediate-high	37	30	67 (14%)
high	11	11	22 (7%)
History of smoking			
no	119	88	207 (43%)
yes	120	53	173 (36%)
unknown	53	43	96 (21%)
Hypertension			
no	266	173	439 (92%)
yes	18	8	26 (5%)
unknown	8	3	11 (3%)
Stem cell transplantation			
no	256	164	420 (88%)
yes	36	20	56 (12%)
Radiotherapy neck			
no	175	112	287 (60%)
yes	104	84	189 (40%)
Radiotherapy mediastinum			
no	215	122	337 (71%)
yes	77	62	139 (29%)
Salvage (any type)			
no	137	98	235 (49%)
yes	155	86	241 (51%)

The overall cumulative incidence (with death by any cause as competing event) of cardiovascular disease (all first events taken together) was 12% at 5 and 22% at 10 years (Fig.1). Cumulative incidence at 10 years of chronic heart failure was 18%, of coronary artery disease 11% and of stroke 7%. At longer follow-up the incidence increased even further without showing any plateau.

Fig.1 Overall cumulative incidence of cardiovascular disease

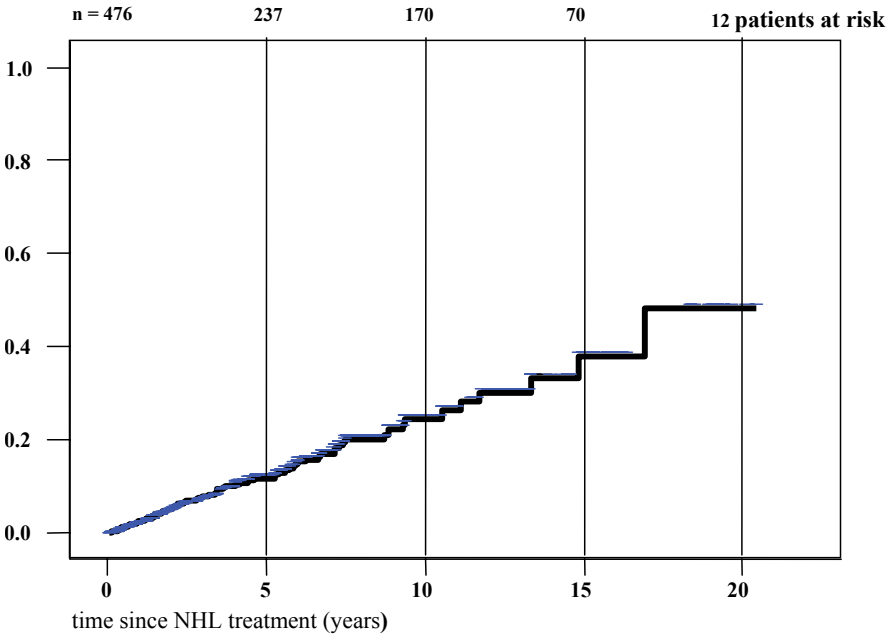


Table 2. Standardized incidence ratios and absolute excess risks of cardiovascular disease after NHL treatment.

	Observed*	Expected	Standard incidence ratio (95%CI)	Absolute excess risk per 10,000 py	Median age at event (range) years	Median interval treatment till event (range) years
Chronic heart failure	64	12.0	5.4 (4.1 to 6.9)	208	53.6 (38-82)	3.4 (2.3-4.6)
Coronary artery disease	20	30.4	0.7 (0.4 to 0.9)	-38	53.1 (34-89)	2.5 (1.8-3.4)
Myocardial infarction	17	14.8	1.2 (0.8 to 2.4)	8	49.3 (38-73)	2.6 (2.0-3.4)
Angina pectoris	16	19.6	0.8 (0.4 to 1.3)	-14	54.1 (34-89)	2.4 (1.8-3.2)
Stroke	11	7.3	1.5 (1.1 to 2.7)	15	62.1 (39-79)	3.7 (1.6-5.1)

*Observed in 476 patients for myocardial infarction (1980-2000) and in 441 patients for chronic heart failure and stroke (1985-2000).

Twelve new strokes were reported after NHL treatment: 11 after (SIR 1.4, 95% CI; 1.1-2.4, AER 15/10,000 person-years) and one before 1985. The median age at the diagnosis of stroke was higher (median 62.1 years) than for cardiac disease (median between 49 – 54 years, Table 2). The median age for all cardiovascular events at occurrence in our cohort was rather young (median between 49 and 62 years of age) as compared to the median age given in the literature (median age between 65 and 75). [40-42] Five cases of peripheral arterial occlusions with disabling intermittent claudication were reported and two aneurysms of the aorta, one occlusion of the a. mesenterica and one stenosis of the v. portae. A SIR for these vascular events could not be estimated, because Dutch incidence rates are not available covering the period of 1980-2000.Of note, both last cases had been treated with abdominal radiotherapy and four of the five patients with disabling intermittent claudication had received radiotherapy on one or both groins. Next, the SIR for stroke has significantly higher in the patients additional irradiated on the neck compared to those not irradiated in this region (Fig.2, SIRs of 2.3 vs. 0.6). Notably, radiotherapy on the mediastinum did not significantly influence risk of cardiac disease when all irradiated patients were taken into account (Fig.3, 4). However, when we performed a subgroup-analysis according to radiation dose, strongly increased risks for chronic heart failure, myocardial infarction and stroke were observed after 40 Gy or more (Table 3). The presence of pre-existent hypertension increased the risk for myocardial infarction (Fig.3, SIR 6.9 vs. 0.8) and chronic heart failure (SIR 22 vs. 4.9). NHL treatment at a young age (SIR 24.8 vs. 2.8, for under 55 and 55 or older, respectively) and salvage treatment (SIR 8.8 vs. 3.4) raised the risk for chronic heart failure as well (Fig.4). Smoking was associated with a higher risk for chronic heart failure, stroke and especially myocardial infarction (Fig 2-4).

Table 3. Standardized incidence ratios (SIR) and absolute excess risks (AER) of cardiovascular disease after NHL treatment including radiotherapy: a cumulative dose-risk relation.

	Number of patients*	Observed	Expected	SIR (95%CI)	AER per 10,000py
Chronic heart failure					
no radiotherapy on mediastinum	311	39	8.9	4.4 (3.1 to 6.0)	167
30 Gy or less	30	5	1.1	4.7 (1.0 to 8.2)	171
30-40 Gy	85	11	1.6	6.8 (3.3-13.3)	232
more than 40 Gy	15	9	0.3	32.0 (13.7 to 57)	932
Myocardial infarction					
no radiotherapy on mediastinum	337	10	11.6	0.9 (0.4 to 1.6)	-8
30 Gy or less	32	1	1.3	0.8 (0.3 to 2.3)	1
30-40 Gy	89	3	2.1	1.4 (0.4 to 4.3)	5
more than 40 Gy	18	3	0.4	7.5 (1.4 to 19.9)	274
Stroke					
no radiotherapy neck	273	3	4.8	0.6 (0.1 to 1.2)	-12
30 Gy or less	48	1	1.4	0.7 (0.1 to 2.7)	-9
30-40 Gy	103	2	0.9	2.2 (0.1 to 3.1)	5
more than 40 Gy	38	5	0.7	8.6 (3.1 to 18.7)	260

*Comparison in 476 patients for myocardial infarction (1980-2000) and in 441 for chronic heart failure and stroke (1985-2000).

Table 4. Standardized incidence ratios (SIR) according to follow-up time: a longer follow-up shows further increase of risk for cardiovascular disease.

SIR (95%CI)	**All patients (median follow-up 8.4 of years n=476)***	**patients with at least 3 years of follow-up (n=305)**	**patients with at least 5 years of follow-up (n=240)**
Chronic heart failure	5.4 (95% CI; 4.1-6.9)	6.2 (95% CI; 4.9-7.9)	7.3 (95% CI; 5.9-12.1)
Myocardial infarction	1.2 (95% CI; 0.8-1.8)	1.5 (95% CI; 0.8-2.6)	1.6 (95% CI; 1.2-6.9)
Stroke	1.8 (95% CI;1.1-2.4)	2.1 (95% CI; 1.4-6.1)	2.5 (95% CI; 1.6-7.9)

*Comparison in 476 patients for myocardial infarction (1980-2000) and in 441 for chronic heart failure and stroke (1985-2000).

In patients with more than 3, respectively 5 year follow-up, higher risks for chronic heart failure were observed. This trend of greater SIRs with longer follow-up was also seen for myocardial infarction and stroke (Table 4). By reviewing cumulative incidence (Fig. 1) this could have been expected, as there was no plateau observed during longer follow-up. Multivariate Cox regression analysis showed excess risk associated with the same factors that emerged from the stratified analyses comparing SIRs. Age at start of NHL treatment was the most important factor determining risk of any cardiovascular event (HR 4.1; 95% CI 2.1-8.9). Pre-existent hypertension (HR 2.1; 95% CI 1.2-6.7) and salvage treatment (any type, HR 2.4; 95% CI 1.9-9.9) did also significantly increase risk for all types of cardiovascular disease. Other significant factors were smoking for coronary artery disease (HR 1.7; 95% CI 1.4-5.6) and radiotherapy of the neck for stroke (HR 1.8; 95%CI 1.3-9.1). Cardiovascular disease was more often seen in NHL patients treated in the earlier trials (HR 0.3; 95%CI 0.1-0.7) running from 1980-1990. To study the independent role of doxorubicin on risk for cardiovascular disease, we needed a cohort only treated with chemotherapy. However, these were on average the patients with the best prognosis. Therefore, comparison of risk due to additional modalities to this group would be biased by the difference in follow-up. We therefore selected those 253 patients who were treated only in the first line. Here, we compared risk after chemotherapy alone to risk after chemotherapy plus other modalities (Table 5). It appeared that chemotherapy alone (which in all cases consisted of doxorubicin-based combinations) was clearly related to an increased risk of chronic heart failure (SIR 3.1, 95% CI; 1.9-4.8), with an AER of 127 excess cases per 10,000 person-years.

Table 5. Standardized incidence ratios (SIR) with 95% confidence interval (95% CI) and absolute excess risks (AER) according to NHL treatment: additional treatment increases risk for cardiovascular disease.

	Number of patients*	Observed	Expected	SIR (95%CI)	AER per 10,000py
Chronic heart failure					
after salvage (any type)	225	38	4.3	8.8 (6.3 to 12.1)	346
after first line only	216	26	7.7	3.4 (2.2 to 4.9)	120
only chemotherapy	162	20	6.4	3.1 (1.9 to 4.8)	127
chemo- and radiotherapy	38	4	1.1	3.6 (1.0 to 9.8)	120
chemotherapy and transplantation	13	1	0.1	7.1 (0.2 to 39.8)	81
chemo-, radiotherapy and transplantation	12	1	0.1	12.5 (0.3 to 69.7)	83
Myocardial infarction					
after salvage (any type)	241	10	6.8	1.5 (0.7 to 2.7)	29
after first line only	235	7	9	0.8 (0.3 to 1.6)	13
only chemotherapy	170	6	6.5	0.9 (0.3 to 2.0)	5
chemo- and radiotherapy	40	1	1.8	0.6 (0.1 to 3.1)	33
chemotherapy and transplantation	13	0	0.5	-	-
chemo-, radiotherapy and transplantation	12	0	0.2	-	-
Stroke					
after salvage (any type)	225	4	3.15	1.3 (0.3 to 3.3)	12
after first line only	216	7	5.1	1.4 (0.6 to 2.8)	8
only chemotherapy	135	2	3.4	0.6 (0.1 to 2.1)	-13
chemo- and radiotherapy	56	5	1.5	3.3 (1.1 to 7.8)	145
chemotherapy and transplantation	15	0	0.1	-	-
chemo-, radiotherapy and transplantation	10	0	0.1	-	-

*Comparison in 476 patients for myocardial infarction (1980-2000) and in 441 for chronic heart failure and stroke (1985-2000).

Fig.2 Standardized incidence ratios and absolute excess risks with 95% confidence intervals for stroke after NHL treatment: risk factor sub-analyses. Comparison of 41 NHL patients treated (from 1985 to 2000) with doxorubicin-based chemotherapy to the Dutch population (as population-based incidences of chronic heart failure were available after January 1, 1985). Subgroups are selected to estimate the impact of age during NHL treatment, smoking, pre-existent hypertension and additional salvage treatment (any type), radiotherapy (RT) of the neck, and autologous bone marrow transplantation (ASCT). (Missing data for smoking in 90 cases and for hypertension in 11 cases)

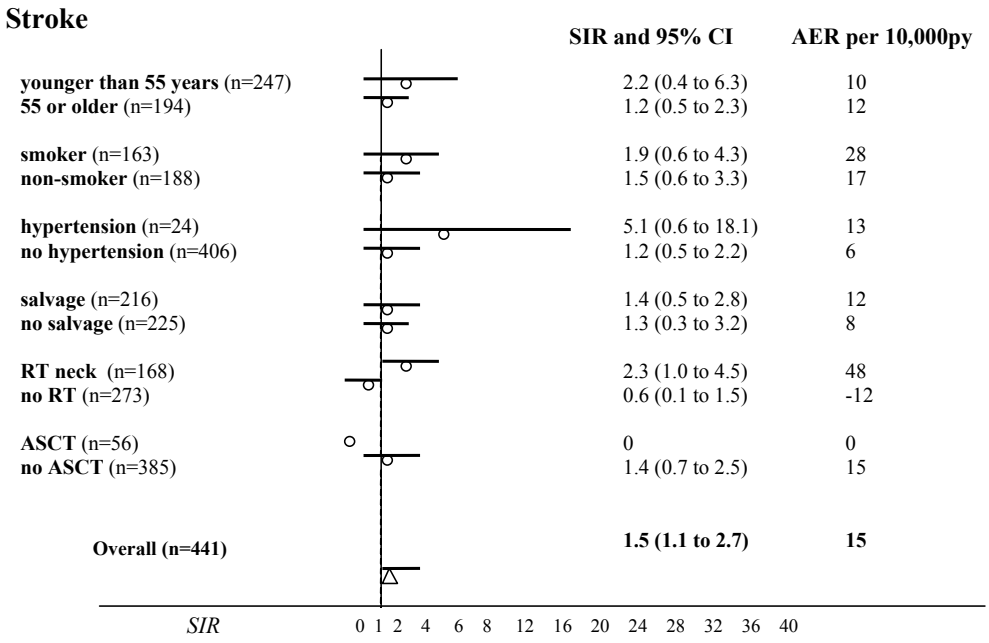


Fig.3: Standardized incidence ratios and absolute excess risks with 95% confidence intervals for chronic heart failure after NHL treatment: risk factor sub-analyses. Comparison of 441 NHL patients treated (from 1985 to 2000) with doxorubicin-based chemotherapy to the Dutch population (as population-based incidences of chronic heart failure were available after January 1, 1985). Subgroups are selected to estimate the impact of age during NHL treatment, smoking, pre-existent hypertension and additional salvage treatment (any type), radiotherapy (RT) of the mediastinum, and autologous bone marrow transplantation (ASCT). (Missing data for smoking in 90 cases and for hypertension in 11 cases)

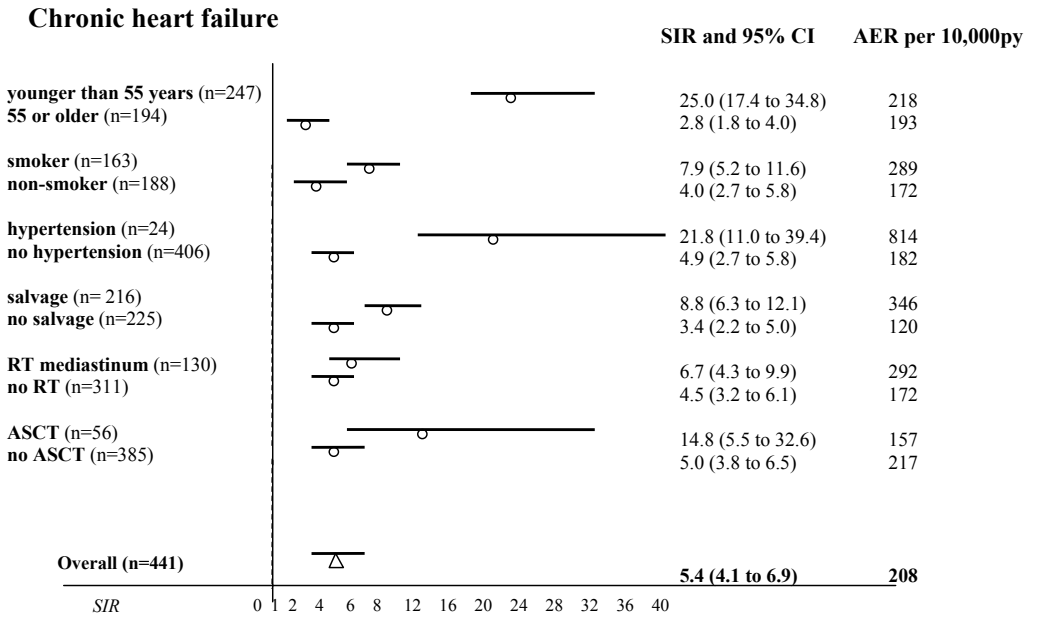
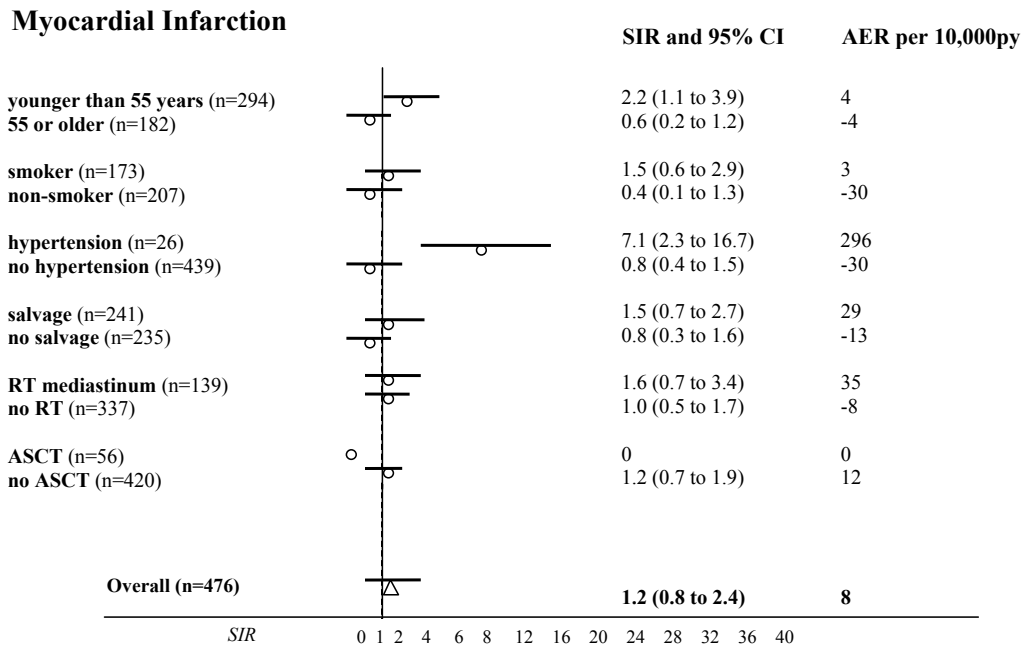


Fig.4: Standardized incidence ratios and absolute excess risks with 95% confidence intervals for myocardial infarction after NHL treatment: risk factor sub-analyses. Comparison of 476 NHL patients treated (from 1980 to 2000) with doxorubicin-based chemotherapy to the Dutch population. Subgroups are selected to estimate the impact of age during NHL treatment, smoking, pre-existent hypertension and additional salvage treatment (any type), radiotherapy (RT) of the mediastinum, and autologous bone marrow transplantation (ASCT). (Missing data for smoking in 96 cases and for hypertension in 11 cases)



Discussion

In comparison with the Dutch population, the risk for chronic heart failure appeared markedly increased in patients treated for aggressive NHL. In contrast, the risk of coronary artery disease matched the general population. Coronary artery disease is considered to be the main cause of chronic heart failure in the general population, whereas valvular disease and cardiomyopathy are far less common causes. [40-42] In our cohort of NHL patients causes other than coronary artery disease were frequently reported: cardiomyopathy (21%) and also rhythm disturbances were far more frequently observed than expected. [31-33, 42] Chronic heart failure (related to left ventricular dysfunction), ECG alterations (rhythm disturbances) and cardiomyopathy have all been described after doxorubicin-containing chemotherapy, not only as early onset complications, but also as late events, observed up to 20 years after completion of anthracycline therapy. [42-45] Unfortunately, detailed information on type of cardiomyopathy (dilated or obstructive), or on kind of rhythm disturbances was not available in our cohort. Nevertheless, we observed a clearly increased risk (Table 5, SIR 3.1, AER 127/10,000 person-years) of chronic heart failure in patients only treated with chemotherapy, even though in most patients the maximum doxorubicin dose of 400 mg/m^2 had not been

exceeded. Coronary artery disease and other vascular occlusive events based on pathological findings of accelerated atherosclerosis have been reported as late complications in Hodgkin's lymphoma patients, who have been mainly treated with radiotherapy. [9-12] Also, fibrosis of the pericard, myocard and valves are described, leading to serious and often life-threatening cardiac events. [46, 47] As more than half of our patients had received additional radiotherapy involving the mediastinum, we had expected more coronary and valvular disease. Remarkably, risk for coronary artery disease in our cohort appeared to be comparable to the Dutch population when both age and gender were taken into account. Only in the small subset of patients who had received 40 Gy or more, an increased risk was observed. Cardiotoxicity due to radiotherapy has been described as appearing late (time-intervals of approximately 7 years before development of clinical signs are reported).[47, 48] To evaluate whether follow-up time did influence the role of radiotherapy, we re-analyzed our data restricted to those patients who had a follow-up of more than 3 or even more than 5 years. In these long-term survivors a relative higher risk for chronic heart failure and myocardial infarction was found, but still no significant influence of mediastinal radiotherapy was observed. We cannot exclude, however, that such an effect of increase in risk may emerge after more prolonged follow-up. Another explanation for the lack of radiotherapy-related cardiotoxicity in NHL may be related to the dose and field size of radiotherapy on the mediastinum. In earlier reports, mainly in Hodgkin's lymphoma patients, often higher doses of radiotherapy had been given (without chemotherapy) and outdated techniques were used. [9-12, 47-50] In our study protocols, the prescribed dose of additional radiotherapy was 30 Gy in case of complete remission and 40 Gy in case of partial response. Dose-reduction was advised in case of large-field and extranodal localizations. After the retrospective collection of all fields and cumulative dose, most of our patients appeared to be treated with 30 to 40 Gy. Furthermore the cumulative radiation dose to the heart region in our cohort was restricted by improved planning techniques including (partial) shielding, which became standard after 1985. [50, 51] In contrast, no blocks or dose-limitations were used in the neck and groins, resulting in higher cumulative doses and indeed higher risk for occlusive vascular disease. Moderate doses (30-50 Gy) increased the risk of stroke after NHL in our cohort, but truly high risks, like described by Dorresteijn et al[52] in patients with head and neck cancer (who received all up to 60 Gy) were not observed. In a rather elderly patient group, risk of cardiovascular disease can only be correctly described if compared to the general population. However, the way in which population-based rates are selected for comparison needs close attention. First of all, incidence rates differ over time: for both chronic heart failure and coronary artery disease the incidence dropped around 20% from 1985 to 1998, probably due to a lower prevalence of risk factors and early intervention strategies in Northern Europe.[21-26] Furthermore, incidences also vary geographically because of differences in access to medical care, but also life-style, socio-economic status and genetic predisposition. [22-24] We therefore obtained population-based data covering the same region and used calendar period-specific rates to account for changes over time in the background rate for our cohort. Thus, the lower incidence rates in the Dutch population during the late nineties did not cause an overestimation of risk among those patients diagnosed in the eighties. The Dutch (CMRN) incidence rates used were prospectively collected in general practices. Similarly as defined in our cohort, the CMRN registers all

different events (and date) even when present in the same person, but in case of more of the same events only the first in time. In both the CMRN and our study occurrence of cardiovascular disease was registered during follow-up. The NHL patients were followed in the routine follow-up of the 4 EORTC-trials, the CMRN cohort by their GP. Because in the Netherlands nearly all residents are followed by their GP and not only those needing medical care the surveillance bias is limited. The only difference is that the study cohort has been retrospectively reviewed, while the CMRN is a prospective registration project since 1971. The ideal way to compare incidence, without surveillance bias would have been a comparison between two cohorts that are both prospectively followed. However, (prospective) studies on late sequelae need long-time follow-up in patients uniformly treated and these data are very rare. The source of information in the study-group was the treating physician, consulting the GP of the patient if the patient was no longer under his medical surveillance at time of the survey in 2002 (mainly because of death). Because of the retrospective nature of the survey, we can not guaranty that the treating physicians actively inquired about cardiovascular disease in all of the patients it selves. However, only hard diagnoses, quoted as serious and disabling were asked to be registered. This implies a selection of patients with serious cardiotoxicity only (and therefore underestimation of cardiovascular disease incidence), but corresponds with the CMRN registration. Hequet et al[53] analyzed a group of adult lymphoma patients treated with doxorubicin-based chemotherapy and found only a single case with overt clinical chronic heart failure out of the 141 patients, but subclinical cardiomyopathy in 39 cases. Adams et al[54] did the same in long-term HL survivors (median follow-up 14.3 years) and also concluded that although most patients are doing fine, subclinical cardiovascular changes are often present and can progress to clinical disease if not treated. If this ratio of chronic heart failure versus subclinical cardiomyopathy would be identical in the long-term follow-up of NHL patients, close monitoring of these patients would be mandatory. Given the fact that most cardiovascular events in our study occurred already in the first years after NHL treatment (median interval around 3 years), we propose that follow-up of NHL patients in this period needs to be focused not only on recurrence of disease but on signs of cardiovascular damage as well. As the cumulative incidence increased only further over time, we would advise to continue follow-up after 5 and even 10 years, if possible. Hopefully life-style advice, especially quitting smoking, and treatment of hypercholesterolemia and hypertension will decrease the impact of treatment-related risk of cardiovascular morbidity and mortality. According to our study, an elevated risk for chronic heart failure can also be expected after full dose doxorubicin-based chemotherapy for other cancer types, like breast cancer. More research in this field, based on long-term follow-up data and comparison to general population incidence rates is needed. In conclusion, NHL patients carry a high risk of chronic heart failure after being cured, and need lifelong monitoring in this regard. In contrast, risk of coronary artery disease appeared more age-dependent than treatment related.

References

1. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst.1993;85:25-31.Haddy TB, Adde MA, McCalla J, et al: Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol.1998; 6:2070-9.
2. Bhatia S, Robinson LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med.1996; 334:745-751. Andre M, Mounier N, Leleu X, et al: Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 2004; 103:1222-8.
3. Aviles A, Diaz-Maqueo JC, Garcia EL,et al. Late lethal events in patients with diffuse large B cell lymphoma, a review of 714 patients treated in a single centre. Leuk Lymphoma 2001; 42:631-7.
4. Moser EC, Noordijk EM, Carde P, et al: Late non-neoplastic complications in aggressive Non Hodgkin's Lymphoma patients across four randomized EORTC-trials. Clin Lymphoma Myeloma. 2005 Sep;6(2):122-30.
5. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA.1993; 270:1949-55.
6. Aviles A, Neri N, Nambo JM, et al. Late cardiac toxicity secondary to treatment in Hodgkin's disease. A study comparing doxorubicin, epirubicin and mitoxantrone in combined therapy. Leuk Lymphoma 2005; 46:1023-8.
7. Gustavsson A, Osterman B, Cavallin-Stahl E, et al: A systematic overview of radiation therapy effects in Hodgkin's lymphoma. Acta Oncol.2003; 42:589-604.
8. King V, Constine LS, Clark D, et al: Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys.1996; 36:881-9.
9. Glanzmann C, Kaufmann P, Jenni R, et al: Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol.1998; 46:51-62.
10. Hull MC, Morris CG, Pepine CJ, et al: Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA.2003; 290:2831-7.
11. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med.1993; 328:1002-6.
12. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, et al: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med.1998; 339:21-6.
13. Aviles A, Delgado S, Fernandez R, et al: Combined therapy in advanced stages (III and IV) of follicular lymphoma increases the possibility of cure: results of a large controlled clinical trial. Eur J Haematol. 2002; 68:144-9.
14. Wilder RB, Rodriguez MA, Tucker SL, et al: Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. Int J Radiat Oncol Biol Phys.2001; 50:743-9.
15. Philip T, Guglielmi C, Hagenbeek A, et al: Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med.1995; 333:1540-5.
16. Milpied N, Deconinck E, Gaillard F, et al: Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med.2004; 350:1287-95.
17. Yeh ET, Tong AT, Lenihan DJ, et al: Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 2004; 109:3122-31.
18. Schimmel KJ, Richel DJ, van den Brink RB, et al: Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev.2004; 30:181-91.
19. Levy D, Kenchaiah S, Larson MG, et al: Long-term trends in the incidence of and survival with heart failure. N Engl J Med.2002; 347: 1397-402.
20. Cowie MR, Wood DA, Coats AJ, et al: Incidence and aetiology of heart failure. A population-based study. Eur Heart J.1999; 20: 421-428.
21. EUROASPIRE I and II Group: Clinical reality of coronary prevention guidelines: a comparison of

EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. Lancet 2001; 357:995-1001.
22. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, et al: Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet 2000; 355:675-87.
23. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, et al, for the WHO MONICA Project: Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. Lancet 2000; 355: 688-700.
24. Empana JP, Ducimetiere P, Arveiler D, et al: Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J. 2003; 21:1903-11.
25. Paul I, Bilge A, Bolly F, Boland J, et al: Pilot study for the registration of acute myocardial infarction in the Liege area (Belgium). Rev Epidemiol Sante Publique.2001; 5:423-9.
26. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med.1993; 329: 987-94.
27. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978-1994. Eur Heart J.1998; 19:429-434.
28. Lisdonk van de EH, Bosch van den WJHM, Huygen FJA, Lagro-Jansen ALM. Ziekten in de huisartspraktijk (3e druk). Maarssen: Elsevier/Bunge;1999.
29. Gijssen R, Poos MJJM: Achtergronden en details bij cijfers uit huisartsenregistraties. Gezondheid en ziekte\ ziekte en aandoeningen\hartvaatstelsel\coronaire hartziekten. Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven, RIVM; 2003. http:www.rivm.nl/vtv/object_document/o3171nl7964.html.
30. Somers R, Carde P, Thomas J, et al: EORTC study of non-Hodgkin's lymphoma: phase III study comparing CHVmP- VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. Ann Oncol 1994; 5:S85-S89.
31. Meerwaldt JH, Carde P, Somers R, et al: Persistent improved results after adding vincristine and bleomycin to a cyclophosphamide/hydroxorubicin/Vm-26/prednisone combination (CHVmP) in stage III-IV intermediate- and high-grade non-Hodgkin's lymphoma. The EORTC Lymphoma Cooperative Group. Ann Oncol 1997; 8:S67-70.
32. Carde P, Meerwaldt JH, van Glabbeke M, et al: Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non- Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. The EORTC Lymphoma Group. Ann Oncol 1992; 2:431-5.
33. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al: Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst.2001; 93:22-30.
34. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ.1987; 82:1-406.
35. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc.1958; 53:457.
36. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1988; 16:1141-54.
37. Cox DR: Regression models and life-tables. J Royal Stat Soc Ser B.1972; 334:187-202.
38. Koek HI, Van Leest LATM, Verschuren WMM, et al: Cardiovascular disease in the Netherlands 2004, details on life-style- and risk factors, disease and mortality. The Hague, Dutch Cancer Foundation; 2004.
39. Bots ML, Looman SJ, Koudstaal PJ, et al: Prevalence of stroke in the general population. The Rotterdam Study. Stroke.1996; 9:1499-501.
40. Fox KF, Cowie MR, Wood DA, et al: Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J.2001; 22:228-36.
41. Shan K, Lincoff AM, Young JB: Anthracycline-induced cardiotoxicity. Ann Intern Med.1996; 125:47-58.

42. Limat S, Demesmay K, Voillat L, et al: Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma. Ann Oncol.2003; 2:277-81.
43. Swain M, Whaley FS, Ewer MS: Congestive heart failure in patients treated with doxorubicin. Cancer.2003; 97:2869-79.
44. Steinherz LJ, Steinherz PG, Tan CT, et al: Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA.1991; 266:1672-7.
45. Grenier MA, Lipshultz SE: Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol.1998; 25:S72-S85.
46. Brosius FC, Waller BF, Roberts WC: Radiation heart disease: analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med.1981; 70:519-30.
47. Veinot JP, Edwards WD: Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol.1996; 8:766-73.
48. Zinzani PL, Gherlinzoni F, Piovaccari G, et al: Cardiac injury as late toxicity of mediastinal radiation therapy for Hodgkin's disease patients. Haematologica.1996; 81:132-7.
49. Constine LS, Schwartz RG, Savage DE, et al: Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. Int J Radiat Oncol Biol Phys.1997; 39:897-906.
50. Dorresteijn LD, Kappelle AC, Boogerd W, et al: Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. J Clin Oncol 2002; 20:282-8.
51. Hequet O, Le QH, Moullet I, et al: Sub clinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol.2004; 22:1864-71.
52. Adams MJ, Lipsitz SR, Colan SD: Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol.2004; 22:3139-48.

Chapter 6

Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study.

E.C. Moser, E.M. Noordijk, F.E. van Leeuwen, J.W Baars, J Thomas, P Carde, J.H Meerwaldt, M.M.B van Glabbeke and J.C. Kluin-Nelemans

Haematologica 11, November 2006

Abstract

Background and objective: Second cancer has been associated with Non-Hodgkin's Lymphoma (NHL) treatment, but few studies addressed risk according to specific treatments.

Design and methods: We estimated risk by standardized incidence ratios (SIR) and absolute excess risk (AER) based on general population rates (European Network of Cancer Registries) in 748 patients (aged 15-82 years) treated for aggressive NHL in 4 successive EORTC (European Organization for Research on Treatment of Cancer) trials.

Results: All patients received fully-dosed CHOP-like chemotherapy, 65% received involved-field radiotherapy and 14% high dose treatment. Half of the patients needed salvage treatment, 37% were followed for >10 years. Cause of death was NHL in 79% of the patients; 4% died of second cancer (median survival 8.9 (0.8-20.5) years). Cumulative incidences (death by any cause as competing event) were 5% and 11% for solid cancer and 1% and 3% for AML/MDS at 10 and 15 years, respectively. Cancer risk appeared age-related: in young patients high risks were observed for leukaemia (SIR 16.7, 95% CI 1.4-93.1, AER 5.0), Hodgkin's lymphoma (SIR 60.1, 95% CI 12.4-175.2, AER 15.7), colorectal (SIR 12.5, 95% CI 2.6-36.5, AER 14.7) and lung cancer (SIR 15.4; 95% CI 4.2-39.4, AER 19.8), while risk in patients older than 45 years matched the normal population. Cancer risk was significantly raised by smoking and salvage treatment.

Interpretation and conclusions: Half of the patients die of aggressive NHL before acquiring sufficient follow-up to experience second cancer risk. Only young patients encounter high second cancer risk during follow-up beyond 10 years.

Introduction

Nowadays, many patients with malignant lymphoma become long-term survivors. During follow-up, therapy-related late sequelae have become an important issue. Secondary cancers were the first late sequelae to be noticed in Hodgkin's Lymphoma survivors. [1-3] After extended reviews on cancer risk after Hodgkin's disease, reports on patients treated for Non-Hodgkin's lymphoma (NHL) have been published as well.[4-12] Most studies report high second cancer risk (2-8 fold), mainly due to high incidence of leukaemia, bladder and lung cancer observed after NHL treatment. In the different publications, the magnitude of second cancer risks varies substantially. Reports on the influence of age at first NHL treatment on second cancer risk are conflicting. [5-12] Cancer risk in elderly NHL patients has never been well defined, as most data available originate from clinical trials limited to the age of 60 years. In a large French study, late sequelae were related to first line doxorubicin-based chemotherapy consistently used in patients treated for aggressive NHL, but unfortunately follow-up did not extend much longer than 10 years. [11] Only two studies reported cancer risk after NHL treatment beyond 15 years. [5, 12] Travis *et al* described a persistently high risk for all cancers over prolonged follow-up periods, while Mudie *et al* mentioned leukaemia and lung cancer in particular. In all reports, factors containing treatment-details (dose, fields) and smoking history were not taken into account. [5-12] Moreover, all different NHL categories were lumped together without central pathology review being part of the selection process. The availability of a large EORTC (European Organization of Research and Treatment of Cancer) database of patients with aggressive NHL, consistently treated with CHOP-like chemotherapy at an age ranging from 15 to 82 years at initial NHL diagnosis, offered the possibility to explore second cancer risk in a well defined NHL patient population of *all* adult ages. Detailed information on type, dose and fields of first line and salvage treatment but also on smoking history, made it possible to evaluate excess risk according to specific treatments and demographic factors.

Design and Methods

Data collection procedures

A retrospective cohort study was performed in 974 patients with advanced aggressive NHL enrolled in 4 successive EORTC trials (1980-1999) mainly in the Netherlands, Belgium, France and Italy. Patient records were reviewed by the local investigators (see appendix A). For details related to the specifically designed case record forms, see Moser *et al*.[13] All trials were designed for intermediate or high grade NHL, all histology was centrally reviewed. Approval of the study was obtained from the EORTC Protocol Review Committee and from all local institutions. Informed consent was provided according to the Declaration of Helsinki. We restricted the analyses to those patients treated with at least 6 cycles of CHOP-like chemotherapy and with a minimal follow-up time of 0.5 year after the end of first line treatment.

General population rates

In this study, we used data derived from the EUROCIM database (version 4) registered by the ENCR (European Network of Cancer Registries).[14, 15] The crude incidence rates provided

by the Eindhoven Cancer Registry up to 1990 and from the Netherlands Cancer Registry for the period of 1990 to 1998 (by 3-years moving averages) were related to the patients treated in the Netherlands (n=291). For the Belgian patients (n=185), the same rates were used for the years 1980-1992, while for the period 1993-1998 the rates provided by the Belgian National Cancer Registry could be used, covering mainly the Flemish region, as the NHL patients originated from institutions in Antwerp, Leuven, Brussels and Tournai. For the French patients (n=143) treated in Rouen, Caen and Paris, we used the crude rates provided by the cancer registries in the Somme, Calvados and La Manche region (1978-1997) and for the Italian patients (n=129, from Ravenna and Aviano) rates from the cancer registries of the Venetian, Parma and Umbrian region (1978-1997).

Definitions

According to the definitions used in the EUROCIM database, we used diagnoses per tumour-site rather than pathology, based on the International Classification of Diseases 9th Edition (ICD9 coding).[14, 15] Cancers of the bone and soft tissue, upper gastro-intestinal tract, genital tract, nervous system, melanoma or myeloma were not observed in the NHL cohort. In one patient, chronic lymphoid leukaemia was diagnosed together with recurrent NHL. This event was excluded from the analyses because of the assumed closely related pathogenesis. Non-melanoma skin cancer (NMSC) and myelodysplastic syndrome (MDS) were registered as events, but no population-based rates were available to estimate excess risk. In the person-years analysis of solid cancer risk all solid cancers, except NMSC were combined; leukaemia risk did not include MDS or lymphocytic leukaemia.

Treatment

Most patients (75%) received the CHVmP/BV regimen given in all 4 trials (consisting of cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin and vincristine).[16-18]Other first lines regimens were CHVmP (CHVmP/BV without bleomycin and vincristin) in the first and ProMACE-MOPP (consisting of prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine) in the second trial. [16, 17] No cumulative total dose doxorubicin-complication relation could be estimated, because dose information of salvage treatment was often lacking. In contrast, details on radiotherapy could retrospectively be checked and the cumulative dose per field estimated. Regarding study-protocol, radiotherapy consisted of 30 Gy for patients with initially bulky disease (>5 cm) in complete response after first line chemotherapy, and 40 Gy for partial response (in fractions of 1.5-2 Gy). If large fields were needed, a reduction of the field, focusing on the remaining lesion was suggested for the last 4-10 Gy. For extranodal locations dose was limited to 20-30 Gy. In the salvage setting, often the same dose-levels were used.

Statistical Analysis

Incidence of second cancer in the study population was compared to incidence in the Dutch, Belgian, French, Italian population, respectively. In this person-years type of analysis, the ratio of observed and expected number per cancer-type was determined. [14, 15] The observed/expected ratio will further be denoted as the Standard Incidence Ratio (SIR).[19] Expected numbers were computed with the use of age-, sex-, and calendar period-specific incidence

rates derived from the EUROCIM database. Absolute excess risk (AER per 10,000 person-years) was calculated as the observed number of secondary cancer in our cohort minus the number expected, divided by number of person-years at risk, multiplied by 10,000, expressing the number of excess cases per 10,000 person-years diagnosed in the study group compared to the general population. The incidences per person-year were categorized by age in 5-years intervals (running from 15 to 85 years), by sex and by calendar period in 2 to 3 years-intervals (running from 1980 to 2001) in both the study and the EUROCIM cohort. In all patients accumulation of person-time at risk for second cancer began at 0.5 years after end of first line NHL treatment and stopped at date of diagnosis of second cancer, date of death, or most recent information on cancer occurrence, whichever came first. When analyzing one specific cancer, observed numbers were based on all first date of diagnosis of this type of cancer occurring at least 0.5 year after NHL treatment, allowing more than one type of cancer diagnosed per patient in the NHL cohort; correspondingly to the calculation of cancer incidence in the EUROCIM cohort. Confidence limits were calculated using exact Poisson probabilities of (small) observed numbers.[20, 21] Median follow-up, time to occurrence and survival were estimated as a function of time since start of NHL treatment, and analysed according to the product-limit method first described by Kaplan and Meier, censoring for death, lost to follow-up and event (whatever came first). [22, 23] Cumulative incidences were estimated in the competing risk model with death from any cause as competing event. [24, 25] The Cox proportional-hazards model was used to quantify the effects of different treatments on second cancer risk (all malignancies, except NMSC and NHL) *within* the patient group, adjusting for confounders, as opposed to the person-years analysis in which risk is compared with the general population. [26] Forward stepwise confounder selections, in which the effect of adding one confounder at the time was evaluated, was based on a more than 10% change in the risk estimate of the exposure variable of interest, irrespective of significant values. All factors were categorized and the analyses were stratified by trial (since there was a significant survival difference across trials, see Moser *et al*). [27] Cox's models were fitted using SPSS statistical software (SPSS, Inc Chicago, IL).

Results

Within the 4 EORTC trials for advanced aggressive NHL, 864 (91%) patients had been treated in the Netherlands, Belgium, France or Italy. One hundred and twelve patients had a follow-up of less than 0.5 year due to early progression or death. In 748 of the remaining 752 cases follow-up information was complete until death or January 1st, 2001. The quality of the case record forms was excellent with less than 5% missing data. The characteristics of the 748 patients are given in Table 1. The mean age was 49, ranging from 15 to 82 years. Most patients had stage III or IV disease (71%) and a low to intermediate IPI risk profile (70%). Overall received 65% additional radiotherapy, 49% more than one line chemotherapy and 14% stem cell transplantation, preceded by high dose chemotherapy; no total body irradiation had been given (see Table 2). The most common cause of death was NHL (79%), whereas 4% of the patients died of second cancer.

Table 1. NHL patient and overall treatment characteristics

Patient characteristics	**Men** n=456	**Women** n=292	**Total** n=748	**Person-years at risk** 5020
Country				
The Netherlands	181	110	291	2050
Belgium	108	77	185	1237
France	92	51	143	1004
Italy	75	54	129	729
Age				
Younger than 45 years	203	108	291	1882
45 years or older	263	194	457	3138
Ann Arbor stage				
I bulky-II	140	83	223	2022
III-IV	316	209	525	2998
International Prognostic Index				
Low-intermediate	175	93	468	2181
Intermediate	143	109	252	2759
Intermediate-high	69	45	114	290
High	16	14	30	110
History of smoking				
No	205	195	400	1946
Yes	218	83	301	2763
Unknown	33	14	47	311
Follow-up				
5 yrs or less	206	129	335	972
More than 5 yrs	250	163	413	4048
More than 10 yrs	105	115	220	2670
More than 15 years	29	30	59	1768

Cumulative incidences were for solid cancer 5% at 10 years and 11% at 15 years, respectively, and for MDS/AML 1% at 10 years and 3% at 15 years, respectively (median follow-up 9.4 (0.8-20.5) years). Solid cancer incidence in the study cohort started to increase after 10-15 years of follow-up without showing any plateau (Fig.1). The median time interval between end of first line therapy and secondary cancer diagnosis was 5.8 (2.4-6.8) years.

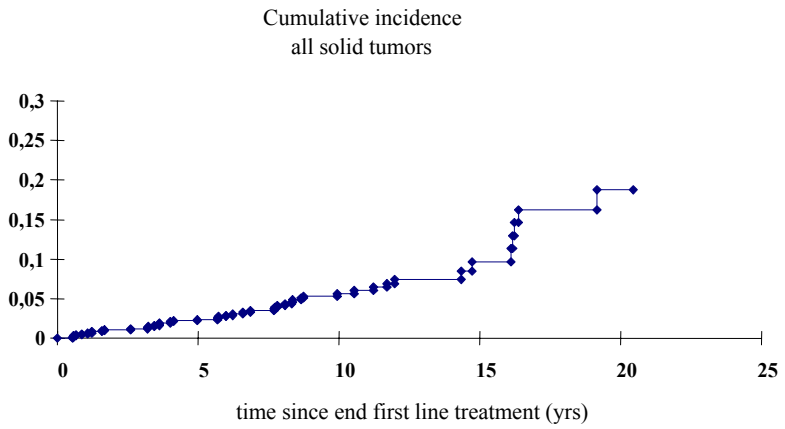


Fig.1 Cumulative incidence (death by any cause as competing risk) of solid cancers, except non-melanoma skin cancer after NHL treatment

Table 2. Overall NHL treatment characteristics (including first line and salvage treatment)

Treatment characteristics	**Cumulative dose**	**Men** n=456	**Women** n=292	**Total** n=748	**Person-years at risk** 5020
Chemotherapy containing					
Doxorubicin	up to 400 mg/m^2	456	292	748 (100%)	5020
Cyclophosphamide	up to 5.2 g/ m^2	456	292	748 (100%)	5020
Bleomycin	up to 80 mg	360	230	590 (79%)	3966
MOPP*	-	205	131	336 (45%)	2259
Cisplatin	-	48	37	85 (11%)	512
Salvage chemotherapy					
First line only		244	138	382 (51%)	2870
Salvage		212	154	366 (49%)	2150
Stem cell transplantation#					
No		392	249	641 (86%)	4273
Yes		64	43	107 (14%)	747
Radiotherapy fields given	Median				
Neck	38 Gy (28-60 Gy)	186	123	309 (41%)	2043
Mediastinum/Axillae	36 Gy (28-56Gy)	126	106	232 (31%)	1523
Abdomen/ Groins	36 Gy (20-42Gy)	166	106	272 (36%)	1888

*MOPP= mechlorethamine, vincristine, prednisone and procarbazine, # stem cell transplantation preceded by high dose chemotherapy, mostly BEAC (consisting of carmustine, etoposide, cytarabine, cyclophosphamide); no total body irradiation had been given

Table 3 shows the person-year analyses comparing the observed and expected second cancers.

A total of 37 solid cancers were observed after NHL treatment (74/10,000 person-years), compared to 38.8 tumours expected (SIR 1.0, 95% CI; 0.7-1.3, AER -3.6). In 12 patients NMSC was observed and half of them had more than one lesion (24/10,000 person-years). Nine cases of MDS were observed (18/10,000 person-years), which progressed in one patient

into acute myeloid leukaemia, diagnosed 3.1 years after first line NHL treatment (3.3; 95% CI 0.08-18.6, AER 1.4). Leukemia risk was not elevated (SIR 1.4, 95% 0.1-7.7). Three cases of Hodgkin's lymphoma were diagnosed (median interval of 2.8 years), while 0.11 were expected (SIR 27.3, 95% CI 5.6-79.7, AER 5.8). Six cases of lung cancer were observed, while 7.9 were expected (SIR 0.8, 95% CI 0.3-1.5, AER -3.8). Six patients were treated for breast cancer, of whom two bilateral with a mean interval of 2.3 years (SIR 1.9, 95% 0.8-3.7, AER 7.4). Thyroid cancer was diagnosed in one patient treated with additional radiotherapy on the neck (30 Gy). Significant risk was observed for bladder cancer, with a burden of 6.6 extra cases per 10,000 person-years of follow-up (SIR 3.0, 95% CI 1.0-6.9). Eight out of the nine patients, who developed MDS had received additional chemotherapy; in five of them this was followed by stem cell transplantation.

Cancer risk appeared to be clearly age-related (Table 4): in young patients significantly higher solid cancer risk was observed with a burden of 20.1 extra cases per 10,000 person-years of follow-up (SIR 3.6, 95% CI 2.0-6.0). High risks were observed for leukemia, Hodgkin's lymphoma, colorectal and lung cancer. No breast cancer cases were observed among patients younger than 45 years at NHL diagnosis, while a two-fold increased risk was observed in elderly patients. Trends for excess solid cancer risk (Table 5) were seen for patients with a follow-up of more than 15 years, smokers and those who received additional (salvage) chemotherapy. The person-years sub-analyses for site-specific solid cancers were underpowered by the small number of events. NHL diagnosis at young age, advanced stage NHL, smoking and additional (salvage) chemotherapy appeared to be significant in the multivariate analysis for second cancer risk (Table 6). In multivariate analysis for AML/MDS risk, young age (<45 years) at NHL diagnosis was the most and only significant factor (Hazard ratio 3.8; 95% CI 1.2-5.7). Trends for excess risk were seen for additional high dose treatment with stem cell transplantation (Hazard ratio 3.6; 95% CI 0.8-8.7) and salvage chemotherapy (Hazard ratio 3.8; 95% CI 0.8-17.7).

Table 3. Observed (Obs) and expected (Exp) cases of second cancer (by ICD9 coding) in the NHL cohort by country calculating Standardized Incidence Risks (SIR) and Absolute Excess Risks (AER) per 10,000 person-years of follow-up (py) per cancer type. (* does not include MDS or lymphocytic leukaemia)

	The Netherlands (n=291)		***Belgium (n=185)***		***France (n=143)***		***Italy (n=129)***		***Total (n=748)***			
Cancer type	**Obs**	**Exp**	**Obs**	**Exp**	**Obs**	**Exp**	**Obs**	**Exp**	**Obs**	**Exp**	**SIR (95%CI)**	**AER**
Leukaemia* ICD9: 205-208	0	0.27	0	0.18	1	0.16	0	0.11	1	0.72	1.4 (0.4-7.7)	**0.6**
Hodgkin's lymphoma ICD9: 201	2	0.04	0	0.03	0	0.02	1	0.02	3	0.11	27.3 (5.6-79.7)	**5.8**
Head & Neck ICD9: 141-149	1	1.48	2	0.77	1	0.59	0	0.40	4	3.24	1.2 (0.3-3.2)	**1.5**
Colorectal ICD9: 153, 154	2	2.15	2	1.30	1	1.12	1	1.08	6	5.65	1.1 (0.4-2.3)	**0.7**
Pancreas ICD9: 157	0	0.37	0	0.22	1	0.20	0	0.18	1	0.97	1.0 (0.03-5.7)	**0.1**
Lung ICD9: 162	2	3.19	1	1.48	1	1.60	2	1.64	6	7.91	0.8 (0.3-1.7)	**-3.8**
Breast ICD9: 174	3	1.78	2	1.18	3	0.76	0	0.56	8	4.28	1.9 (0.8-3.7)	**7.4**
Bladder and urethra ICD9:188, 189.3-9	1	0.72	1	0.41	3	0.31	0	0.25	5	1.69	3.0 (1.0-6.9)	**6.6**
Prostate ICD9: 185	2	1.91	1	1.12	1	0.85	0	0.60	4	4.48	0.9 (0.2-2.3)	**1.0**
Kidney and ureter ICD9:189.0-2	1	0.37	0	0.30	1	0.26	0	0.21	2	1.14	1.8 (0.2-6.3)	**1.7**
Thyroid ICD9: 193	1	0.05	0	0.04	0	0.02	0	0.02	1	0.13	7.7 (0.2-42.9)	**1.7**
Solid cancer ICD9:140-172, 174-199	**13**	**16.3**	**8**	**9.8**	**12**	**8.3**	**2**	**4.3**	**37**	**38.8**	**1.0 (0.7-1.3)**	**-3.6**

Table 4. Standardized Incidence Risks (SIR) and Absolute Excess Risks (AER) per 10,000 person-years of follow-up (py) per cancer type in patients younger than 45 vs. 45 and older at NHL treatment.
(* does not include MDS or lymphoid leukaemia)

	younger than 45 years				45 years or older			
	Obs	**Exp**	**SIR (95% CI)**	**AER**	**Obs**	**Exp**	**SIR (95% CI)**	**AER**
Leukaemia*	1	0.06	16.7 (1.4-93.1)	5.0	0	0.66	0.0 (0.04-4.9)	-2.1
Hodgkin's lymphoma	3	0.05	60.1 (12.4-175.3)	15.7	0	0.06	0.0 (-1.1-0.5)	-0.2
Head & Neck	1	0.44	2.3 (0.1-12.7)	3.0	3	2.80	1.1 (0.2-3.1)	0.6
Colorectal	3	0.24	12.5 (2.6-36.5)	14.7	3	4.91	0.6 (0.1-1.8)	-6.1
Lung	4	0.26	15.4 (4.2-39.4)	19.8	2	7.60	0.3 (0.1-1.0)	-17.8
Breast	0	0.62	0	-3.3	8	3.66	2.2 (1.0-3.7)	13.8
Bladder	1	0.03	33.3 (0.8-186.4)	5.2	4	1.66	2.4 (0.7-6.2)	7.4
Prostate	1	0.04	25.0 (0.6-139.2)	5.1	3	4.44	0.7 (0.1-2.0)	-4.6
Kidney	0	0.06	0	0.3	2	1.08	1.9 (0.2-6.7)	2.9
Solid cancers	14	3.90	3.6 (2.0-6.0)	20.1	13	34.90	0.4 (0.2-0.6)	-69.9

Table 5. Observed (Obs) and expected (Exp) cases of **solid cancer** (except non-melanoma skin cancer) and Standardized Incidence Risks (SIR) and Absolute Excess Risks (AER) analyzed according to smoking history, additional chemo- and radiotherapy, respectively.

	Obs	**Exp**	**SIR (95%CI)**	**AER per 10.000py**
Follow-up				
Less than 5 years	12	15.1	0.8 (0.4-1.4)	-31.9
5-15 years	13	16.6	0.6 (0.4-1.3)	-15.8
More than 15 years	12	7.1	1.7 (0.9-3.0)	27.7
Smoking History				
No	16	23.1	0.7 (0.4-1.1)	-36.5
Yes	21	14.1	1.5 (0.9-2.2)	25.0
Additional chemotherapy				
Only first line	16	15.1	1.1 (0.6-1.7)	3.8
Salvage treatment	31	23.7	1.3 (0.9-1.9)	34.0
Additional radiotherapy on mediastinum				
No	17	21.1	0.8 (0.5-1.3)	-11.7
Yes	20	17.7	1.1 (0.7-1.7)	15.0
Additional radiotherapy on abdomen				
No	21	24.1	0.9 (0.5-1.3)	-9.9
Yes	16	14.7	1.1 (0.6-1.8)	6.9

*MOPP= mechlorethamine, vincristine, prednisone and procarbazine, # stem cell transplantation preceded by high dose chemotherapy, mostly BEAC (consisting of carmustine, etoposide, cytarabine, cyclophosphamide); no total body irradiation had been given

Table 6. Multivariate analysis of occurrence of second cancer (all types, also including MDS but excluding NHL, lymphocytic leukaemia and non-melanoma skin cancer)

Cox proportional hazard model	**Hazard Ratio**	**95% CI lower**	**95% CI upper**
Sex *(M vs. F)*	1.36	0.64	2.91
Smoking *(yes vs. no)*	2.11	1.33	4.11
Age *(<45 years vs. ≥45 years)*	1.91	1.21	4.12
Ann Arbor stage *(I-II vs. III-IV)*	0.32	0.12	0.84
Performance status *(WHO 0-1 vs. >1)*	1.51	0.56	4.82
Extranodal disease *(0-1 vs. > 1 localisations)*	1.72	0.72	4.31
Additional (salvage) chemotherapy *(yes vs. no)*	1.75	1.21	7.70
Additional Stem cell transplantation *(yes vs. no)*	2.21	0.93	15.66
Additional radiotherapy on neck *(yes vs. no)*	0.85	0.62	3.56
Additional radiotherapy on mediastinum *(yes vs. no)*	2.45	0.86	6.25
Additional radiotherapy on abdomen *(yes vs. no)*	2.91	0.97	7.56
Chemotherapy containing bleomycin *(yes vs. no)*	1.82	0.82	3.75
Chemotherapy containing MOPP *(yes vs. no)*	0.89	0.76	1.34

Discussion

This is the first report on the incidence of second cancers throughout all adult age-categories of patients treated for aggressive NHL with fully dosed CHOP-like chemotherapy. Cumulative incidences at 15 years of solid cancer and MDS/AML were 11% and 3%, respectively. Although neither excess solid cancer, nor excess leukaemia risk was observed when all cancers together were 3taken into account, significantly increased cancer-*specific* risks were observed for bladder cancer and Hodgkin's lymphoma in all adult ages. Second cancer risk was clearly age-related; in young patients strongly increased risks were observed while risk in patients aged over 45 when first treated for NHL, matched the general population.

The statistical methods applied for estimation of late events in patients' cohorts is of key-importance. In a disease with a high percentage of death due to recurrences or high age of the patients, any cumulative risk estimated by the Kaplan-Meier method will result in an overestimation of secondary cancers and therefore need correction in a competing risk model. [24, 25] If we would have ignored death as competing risk, the actuarial incidence calculated by the Kaplan-Meier method would have been 15% at 10 years and even 27% at 15 years (Fig. 2). For organ-specific cancer risk estimates population-based incidence rates are needed. Age, sex, environmental and genetic factors influence cancer risk. Moreover,

cancer incidence varies over time. Therefore, person-years analyses per region, but also per calendar period are needed for optimal excess risk estimation.[19]

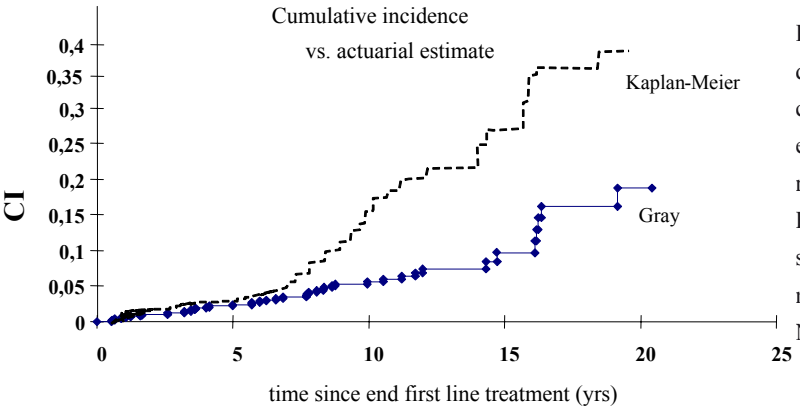


Fig.2 Cumulative incidence (death by any cause as competing risk) estimated in a competing risk model compared to the Kaplan-Meier method of solid cancers, except non-melanoma skin cancer after NHL treatment

Special types of cancers like angiosarcoma or rare other (bone/soft tissue) tumours related to cancer therapy were not observed, except one case of thyroid cancer. Of note, for these types of second tumours 10-20 year induction periods are described, whereas the median follow-up of the EORTC cohort was 9.4 years. [1, 4-6, 28-33] Retrospective scoring of smoking history, radiotherapy doses and fields are needed to evaluate risk factors in cancer risk. These comprehensive data are mandatory, but unfortunately not available in the other large NHL cohort studies.[5-12] In our cohort the role of smoking was evident, but the attribution of infield radiotherapy not significant as described by Travis *et al*, likely due to the small number of events. In a case-control study by Travis *et al* a relationship was found between the cumulative dose of cyclophosphamide and bladder cancer after NHL treatment. [31] We found a three-fold risk of bladder cancer in our cohort, although rather low doses of cyclophosphamide had been given as first line chemotherapy (up to 8x 650 mg/m^2). However, half of the patients received additional chemotherapy as salvage treatment, thereby probably increasing the risk (Hazard ratio 1.75; 95% CI 1.2-7.7) by increased cumulative doses. The role of treatment at young ages has already been emphasized in Hodgkin lymphoma patients. [28, 29, 31, 34] In our cohort, no cases of breast cancer were observed among women treated for NHL before the age of 45. We previously described a high cumulative incidence of premature menopause in our report on late non-malignant sequelae. Probably, the hormonal changes after alkylating chemotherapy protected young patients from breast cancer risk, similar to observations in young Hodgkin's lymphoma patients. [13, 28, 34] By contrast, breast cancer risk appeared elevated in postmenopausal NHL patients (13.8 extra cases per 10,000 person-years of follow-up). [35-38] Two (postmenopausal) women had been treated for bilateral breast cancer (aged 47 and 52 at NHL diagnosis). Unfortunately, relative data on familial predisposition in these women were missing. [39] When addressing cancer risk in relation to treatment modalities, it is important to realize that standard treatments have changed and will change over time. Radiotherapy has been reduced, both in dose and field size, since the introduction of multi-agent doxorubicin-based chemotherapy. In our cohort, patients were all treated by the involved field principle, aiming to reduce late toxicity. Indeed, an overall low cancer risk was observed. [40, 41] As radiation-induced malignancies need time (probably decades) to

develop; prolonged follow-up is needed to conclude whether reduction in radiotherapy dose and fields really leads to a reduction in second tumours. [34, 38, 42-44] Only a minority of our patients received autologous stem cell transplantation as part of first line or salvage treatment. Nevertheless, this treatment modality appeared a potential cancer risk factor in multivariate analysis, especially related to AML/MDS risk. Brown *et al* described a cumulative 10-year second cancer incidence of 21% (median follow-up of 9.5 years) in a NHL cohort all treated with autologous bone marrow transplantation after conditioning with cyclophosphamide and total body irradiation. The second cancers consisted mainly of AML and MDS. [45] In our cohort second haematological malignancies were also observed but to a far lesser extent than in this transplantation cohort, probably because of the fact that no total body irradiations had been given and that relatively low doses of cyclophosphamide had been used.[46] The 10-year solid cancer cumulative incidence rate given by Brown *et al* with death as competing risk in transplanted patients was 10%, but included NMSC as well. In our cohort, the solid cancer risk of 4% increased up to 12% if NMSC had been included. However, population-based skin cancer incidence rates are scarce and often unreliable, as these lesions are commonly removed without histology confirmation and therefore not registered. Therefore, we left these events out of the analyses. The same held true for the diagnosis MDS, which is often based only on cytology, and is severely underscored, in cancer registries, if at all present.

In conclusion, data from this large EORTC cohort show that mainly young patients with aggressive NHL and treated with CHOP-like chemotherapy are at risk for second cancer, whereas most elderly patients die before acquiring sufficient follow-up to experience second cancer risk. Data from older studies have to be interpreted with caution regarding the statistical models used and the lack of details on both treatment and demographic factors analysed.

References

1. Hancock SL, Hoppe RT. Long-term complications of treatment and causes of mortality after Hodgkin's Disease. Semin Radiat Oncol. 1996;6:225-42.
2. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993; 85:25-31.
3. Bhatia S, Robinson LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med.1996; 334:745-51.
4. Swerdlow A.J, van Leeuwen F.E. Late effects after treatment for Hodgkin's Lymphoma. in Dembo A.J, Linch D.C, Lowenberg B (eds): Textbook of Malignant Hematology. Abingdon, United Kingdom, Taylor & Francis, 2005:753-68.
5. Travis L.B, Curtis R.E, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's Lymphoma. J Natl Cancer Inst 1993; 85:1932-7
6. Haddy TB, Adde MA, McCalla J, et al: Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol.1998; 6:2070-9.
7. Brennan P, Coates M, Armstrong B, Colin D, Boffetta P. Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. Br J Cancer 2000;82:1344-7.
8. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer. 2001;85: 997-1005.
9. Ellis M, Lishner M. Second malignancies following treatment in non-Hodgkin's lymphoma. Leuk Lymphoma. 1993;9: 337-42.
10. Okines A, Thomson CS, Radstone CR, Horsman JM, Hancock BW. Second primary malignancies after

treatment for malignant lymphoma.Br J Cancer. 2005;93:418-24.
11. Andre M, Mounier N, Leleu X, et al: Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 2004; 103:1222-8.
12. Mudie N.Y, Swerdlow A.J, Higgins C.D, Smith P, Qiao Z, Hanock B.W, et al. Risk of secondary malignancy after Non-Hodgkin's Lymphoma: a British cohort study. J Clin Oncol 2006; 24:1-6
13. Moser EC, Noordijk EM, Carde P, et al. Late non-neoplastic events in patients with aggressive non-Hodgkin's lymphoma in four randomized European Organisation for Research and Treatment of Cancer trials. Clin Lymphoma Myeloma. 2005;6: 122-30.
14. Tyczynski JE , Démaret, D.M. Parkin DM. Standards and Guidelines for Cancer Registration in Europe, IARC Technical Publication No. 40, IARC Press, 2003
15. Ferlay J, Bray F, Sankila R, Parkin DM. EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union 1998, version 5.0. IARC Cancer Base No. 4. Lyon, IARC Press, 1999. Available from URL: http://www.encr.com.fr/encr.htm
16. Somers R, Carde P, Thomas J, et al. EORTC study of non-Hodgkin's lymphoma: phase III study comparing CHVmP- VB and ProMACE-MOPP in patients with stage II, III, and IV intermediate- and high-grade lymphoma. Ann Oncol 1994; 5:S85-S89.
17. Carde P, Meerwaldt JH, van Glabbeke M, et al. Superiority of second over first generation chemotherapy in a randomized trial for stage III-IV intermediate and high-grade non- Hodgkin's lymphoma (NHL): the 1980-1985 EORTC trial. The EORTC Lymphoma Group. Ann Oncol 1992; 2:431-5.
18. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst.2001; 93:22-30.
19. Van Leeuwen FE, Travis LB: Second cancers, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott Williams & Wilkins, 2005; 2575-2602
20. Liddell FD. Simple exact analysis of the standardised mortality ratio. Journal of Epidemiology and Community Health 1984;38:85-8
21. Silcocks P. Estimating confidence limits on a standardised mortality ratio when the expected number is not error free. Journal of Epidemiology and Community Health 1994;48:313-7
22. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ.1987; 82:1-406.
23. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc.1958; 53:457.
24. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1988; 16:1141-54.
25. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18:695-706.
26. Cox DR: Regression models and life-tables. J Royal Stat Soc Ser B.1972; 334:187-202.
27. Moser EC, Noordijk EM, van Glabbeke M, Teodorovic I, de Wolf-Peeters C, Carde P,et al. Long-term efficacy of the CHVmP/BV regimen used for aggressive non-Hodgkin's lymphoma in three randomised EORTC trials. Eur J Cancer. 2004;40: 474-80.
28. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. 2002; 20:3484-94.
29. Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000;18: 498-509.
30. Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, et al. Late Effects Study Group.High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol. 2003;21:4386-94.

31. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation.
32. Int J Radiat Oncol Biol Phys. 1995;31: 1165-70
33. Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94: 182-92.
34. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst. 1995;87: 524-30.
35. van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst. 2003;95: 971-80.
36. Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. Blood. 2005;106: 3358-65.
37. Koontz BF, Kirkpatrick JP, Clough RW, Prosnitz RG, Gockerman JP, et al. Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. J Clin Oncol. 2006;24: 605-11.
38. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst. 2005;97: 1428-37.
39. Zellmer DL, Wilson JF, Janjan NA. Dosimetry of the breast for determining carcinogenic risk in mantle irradiation. Int J Radiat Oncol Biol Phys. 1991;21: 1343-51.
40. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst. 1999;91: 1310-16.
41. Rosenberg SA, Kaplan HS. Clinical trials in the non-Hodgkin's lymphomata at Stanford University experimental design and preliminary results. Br J Cancer. 1975; 31(Suppl 2): 456-64
42. Burgers J.M.V., Somers R., Quasim M.M. and van Glabbeke M. Report on the EORTC lymphoma trial 20751. Int. J. Radiat. Oncol. Biol. Phys.1983;9: 11–5.
43. Dasu A, Toma-Dasu I, Olofsson J, Karlsson M. The use of risk estimation models for the induction of secondary cancers following radiotherapy. Acta Oncol. 2005; 44: 339-47.
44. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT.
45. Int J Radiat Oncol Biol Phys. 2003;56: 83-8.
46. Kamath SS, Marcus RB Jr, Lynch JW, Mendenhall NP. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma.Int J Radiat Oncol Biol Phys. 1999;44: 563-8.
47. Brown JR, Yeckes H, Friedberg JW, Neuberg D, Kim H, Nadler LM, Freedman AS. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol. 2005;23: 2208-14.
48. Travis LB, Curtis RE, Stovall M, Holowaty EJ, van Leeuwen FE, Glimelius B, et al. Risk of leukemia following treatment for non-Hodgkin's lymphoma. J Natl Cancer Inst. 1994;86: 1450-7.

Chapter 7

Summary and general discussion

Summary and general discussion

For decades lymphoma patients are, whenever possible, treated in large randomised clinical trials. This thesis is based on 30 years experience of large clinical trials by the EORTC (European Organization for Research and Treatment of Cancer) Lymphoma Group in aggressive non-Hodgkin's lymphoma (NHL).[1]

The EORTC Lymphoma Group performed 4 successive trials for advanced aggressive NHL between 1980 and 1999 and all data were collected at the EORTC Data Centre in Brussels, Belgium. Although CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy has been the golden standard therapy for many years, the EORTC used a modification of this scheme, namely the CHVmP/BV regimen (cyclophosphomide, doxorubicin, teniposide and prednisone with bleomycin and vincristine). The consistent use of CHVmP/BV in 4 successive trials offered a unique possibility to update the almost 1000 patients enrolled and evaluate the long-term efficacy and late toxicity of this doxorubicin-based regimen and additional treatments.

Several different regimens have been applied in patients with advanced aggressive NHL. The most illustrative trial has been published by Fisher *et al* [2] comparing third generation regimens (m-BACOD, ProMACE-CytaBOM, MACOP-B) with classical CHOP, showing no benefit of more complex regimens. Our findings (**chapter 2**) were similar when we compared ProMACE-MOPP with the CHVmP/BV regimen. However, by adding bleomycin and vincristine to the CHVmP scheme, survival outcome was significantly improved. Fisher *et al* [2] described a 3 years overall survival of 54% for the CHOP regimen. In our update, an overall survival of 59% at 5 years was observed with the CHVmP/BV regimen, suggesting a more efficient treatment by adding bleomycin and teniposide to classical CHOP. Although the only way to prove the superiority to CHOP is in a randomized trial, we felt/concluded that CHVmP/BV seems at least equivalent to classical CHOP.
Remarkably, survival after CHVmP/BV improved across trials, even after stratifying for the (retrospectively estimated) international prognostic index (IPI). Especially patients treated in the 20901 EORTC-trial (1991-1995) did better than those treated with the same CHVmP/BV regimen in the trials running from 1980-1990 (20802 and 20855). This finding could not be explained by improvement of salvage treatment during the last decade. Bias appeared responsible: stepwise correction for small differences in inclusion criteria eliminated the difference in outcome, especially when histology subgroups were studied. Histology subgroups of aggressive NHL included in the 4 EORTC-trials appeared as important as the IPI consisting of 5 risk factors, published in 1993 and which has been later validated as an important prognostic tool in aggressive NHL. [3, 4]
Description of the analysis of long-term efficacy in **chapter 2** underlines the risk of retrospective subset analyses and the bias introduced when recent studies are compared to older ones. Time and selection are the most important factors inducing bias in estimation of long-term efficacy. Changes in the spectrum of patients due to stage migration, better selection, more supportive care, or altered referral patterns will favour the most recently treated group and can exaggerate the apparent benefit of new treatments.

Until the 1980s, the majority of patients with aggressive NHL were treated with radiotherapy. After introduction of polychemotherapy, extended fields were reduced to 'involved-field' radiotherapy (covering only the region of the initially enlarged nodes). With the introduction of CHOP-like regimens, radiotherapy indications were reduced to bulky disease, residual or progressive disease.
In the 4 EORTC protocols, radiotherapy was prescribed in case of a *partial remission* (PR) after 8 cycles to a dose of 40 Gy (in 1.5-2 Gy fractions) on the region of residual disease. In patients in *complete remission* (CR), radiotherapy (involved field radiotherapy of 30 Gy) was prescribed *only* in case of initial bulky disease (> 5cm) or slow response defined as 50-99% response after 3 cycles. This consolidation radiotherapy in CR patients was also named 'iceberg' irradiation, addressing the fact that fields often covered the region of initial bulky disease. The benefit of consolidation radiotherapy was questioned in the 20932 EORTC-trial. Unfortunately, this trial had to be closed because of lack of accrual. This underlines the current opinion that firstly radiotherapy will not sufficiently contribute to overall survival (e.g. based only on retrospective survey) [5] and secondly might introduce severe late toxicity. The latter is based on late toxicity reports of old trials, performed with the use of extended fields and outdated radiotherapy techniques. Nowadays, new imaging tools (including PET-CT) are integrated in radiation planning systems and along with sophisticated radiation delivery techniques (e.g. IMRT and respiratory gating), permit restriction of radiation fields with increased accuracy. For example, in the new EORTC Hodgkin's lymphoma trials, radiation fields are restricted to 'involved *node*' radiotherapy, covering exclusively the initially involved lymph nodes. With this restricted but moreover modern radiotherapy given complementary to up-front chemotherapy, a significant decrease in late normal tissue complications can be expected.[6, 7]

Chapter 3 focuses on the role of radiotherapy in patients obtaining a PR after 8 cycles of first line chemotherapy. Out of the 842 patients, evaluated after 8 cycles in the 4 EORTC-trials, 227 had obtained a PR and were accordingly treated. When outcomes in CR, PR or response less than 50% or progressive disease (the latter two taken together as progressive disease, PD) were compared, it appeared that patients in PR had a relatively favourable prognosis, much better than PD patients. In many studies, patients in PR are lumped together with PD patients, categorized as "failures" and therefore offered the same salvage treatment. In our opinion, PR patients have to be seen as a separate group and treated accordingly. After publication of the PARMA-study (successful autologous stem cell transplantation (ASCT) in relapsing aggressive lymphoma), the standard treatment for *recurrent* disease (relapse) consists of high dose chemotherapy followed by ASCT. [8, 9] It is important to realise that the PARMA-study was neither designed for patients in PR, nor can the results obtained be extrapolated to this subgroup. All selected patients in the PARMA-study had to be chemosensitive and more than half of them additionally received radiotherapy before transplant. The few patients analysed from the PARMA-study with a relapse shortly after first line therapy and those with a high IPI at time of recurrence, all did very poorly, also with ASCT.[10, 11]
It is debatable, if an aggressive approach as ASCT is needed in case of PR. If local radiotherapy

can convert a PR directly after first line chemotherapy into a durable CR, this would be a far less toxic alternative. Moreover, in case of lacking response to radiotherapy or progression, high dose chemotherapy can anyhow be started without excess toxicity or delay.[12, 13]
In the absence of any randomised trial addressing PR patients, we evaluated the 227 PR patients treated within 8 weeks after the 8th cycle of first line chemotherapy: 114 received involved field radiotherapy, 93 second line chemotherapy, 16 ASCT and four underwent surgery. The median progression-free survival in PR patients was 4.2 years and 48% remained progression-free at 5 years. Half of the PR patients converted to a CR. After conversion, survival was comparable to patients directly in CR. Radiotherapy resulted in better overall and progression-free survival compared to other treatments. Correction by multivariate analysis for prognostic factors showed that radiotherapy was undoubtedly the most significant factor affecting survival outcome. As the EORTC protocols prescribed radiotherapy for all patients in PR, not many were treated with ASCT. Moreover, our data originate from trials since 1980 and it was not before the early nineties that ASCT was introduced as first salvage treatment. Obviously, no comparison of radiotherapy versus ASCT could be made given the absence of any randomised setting and low number of patients transplanted. What can be said is that outcome after radiotherapy was superior to second line chemotherapy only. The data strongly suggest, moreover, that PR patients with initial low to intermediate IPI, bulky disease or nodal disease only, can be very well salvaged by involved field radiotherapy. Assessment in a cross-over designed randomised trial (radiotherapy versus ASCT) seems more than justified. However, to answer this question today, a coalition of several Lymphoma Groups will be needed, given the limited number of patients.

Evidently, the definition of PR – although not changed during the years as far as measurements are concerned – has gained in quality by modern imaging techniques. Although in our cohort residual localisations were measured and scored in detail, and in case of doubt cytology or histology had to be performed, one has to realize that PET was not yet routinely used. PET, particularly using [^{18}F]fluorodeoxyglucose (FDG), has recently emerged as a powerful functional imaging tool in NHL. Numerous investigations have been reported on its use for (re)staging and monitoring tumour response. Even attempts to distinguish between indolent and aggressive NHL by difference in FDG uptake are reported. [14] In staging, PET can provide complementary information to CT and histological biopsy, with potential modification of stage (usually upstaging) and impact on management. [15-17] In restaging, PET can distinguish between viable tumour and necrosis or fibrosis in the residual mass(es) often present without any other clinical or biochemical evidence of disease.[18-20] This use is probably the most important one and has diminished the role of unconfirmed CR (CRu) in the new guidelines incorporating PET-based response designations. [21] However, false-positive findings may be seen, due to rebound thymic hyperplasia or post-therapy inflammatory changes, with the latter apparently more frequent following radiation than immuno-chemotherapy.[20, 21] Longer delay of imaging after radiation is therefore advocated, but not yet exactly defined. Post-therapy surveillance without conventional control remains controversial, because of the false-positive findings, potentially resulting in increased costs without proven benefit by early detection compared to standard surveillance methods. [22] Large prospective studies

are, therefore, needed to determine whether routine PET is cost effective and can result in meaningful improvement of patient outcome. The role of PET in monitoring *disease* during treatment is evolving. An early scan after 2-4 cycles of chemotherapy showing a rapid decline of FDG uptake can preview a higher chance of durable CR at the end of treatment and can probably be used to tailor treatment in the near future.[23-27]
PET becomes more and more available for imaging and radiation treatment planning and can accordingly be implemented in large clinical trials. PET or moreover PET-CT is likely to emerge as the pre-eminent tool in NHL imaging enabling an integrated functional-anatomic tumour assessment with favourable impact on patient management and, possibly, outcome.[21- 28]

As the CHVmP/BV regimen has been the standard for more than 20 years, the EORTC database afforded the unique possibility to explore the late complications of this regimen and additional treatments. Of the 951 patients randomised, complete data on late effects could be collected in 757 patients, who were selected having received at least 6 cycles of first line chemotherapy and were followed for at least half a year and yearly afterwards (median follow-up 9.4 (2.1-20.4) years). Many late non-neoplastic events (**chapter 4**) were observed: 46% of the patients encountered one or more late events. At 15 years, the cumulative incidences (with death by any cause as competing event) of cardiac disease and premature menopause were 20% and 29%, respectively. Renal insufficiency (11%), newly acquired hypertension (8%) and disabling neuropathy (13%) were also frequently seen. Salvage treatment was a risk factor in most events. Smoking and pre-existent hypertension were the main risk factors for cardiovascular disease. In-field radiation therapy was related to hypothyroidism, lung fibrosis, hypertension, gastro-intestinal toxicity and renal insufficiency, but not to cardiovascular events, when dose levels did not exceed 30-40 Gy. ASCT, cisplatin and MOPP-containing chemotherapy (mechlorethamine, vincristine, prednisone and procarbazine) were associated with infertility and renal insufficiency.
Altogether, half of the long-term survivors encountered late complications of NHL treatment, hampering quality of life and even contributing to early death. If all late events observed can be addressed as complications of treatment remains, however, to be seen; age, smoking and hypertension are known risk factors in the normal population as well. Only few reports on late toxicity in NHL include non-neoplastic events.[29-31] In relating risk to treatment, retrospective scoring of demographic (including smoking history) and (salvage) treatment factors (including dose and fields) is mandatory, but unfortunately not available in the other large NHL cohort studies.[29-32]

The statistical methods applied for estimation of late events in patients' cohorts are evolving and of key-importance. In patients with moderate to poor prognosis or of old age, any cumulative risk estimated *within* the patient cohort by the Kaplan-Meier method will result in an overestimation and therefore need correction in a competing risk model.[33-36] For disease specific risk estimates, population-based incidence rates are needed. Age, sex, environmental and genetic factors influence risk. Moreover, incidence rates vary over time. Therefore, person-years analyses per geographical region or country, but also per calendar

period are needed for optimal excess risk estimation. [37] In cancer, many regional and nation-wide registries already exist. In non-neoplastic disease, however, regional registration studies are scarce and diagnosis definitions are less worldwide accepted. In the Netherlands, the unique situation exists that almost all residents are followed by a general practitioner (GP) and not only those needing medical care. The GP receives all medical correspondence from attending physicians regarding their patients and is the official person to access specialized medical care. Hence, the dataset of the *Continuous Morbidity Registry Nijmegen* (CMRN) consists of the entire primary health care provided to the population as well as referrals for health care. [38, 39] The outcome of interest of the CMRN is estimating incidence of the most common diseases in the general population. As incidence rates are registered by the CMRN according to age, sex and per calendar period, this registry can be very well used for person-years analyses of patients treated in the Netherlands or Belgium.[38-40]

As cardiovascular disease was one of the most frequently observed late complications after NHL therapy, the CMRN was used to estimate risk of NHL patients compared to the normal population. In **chapter 5**, we calculated standardized incidence rates (SIRs) and absolute excess risks (AERs) based on CMRN rates in 476 (Dutch and Belgian) patients treated with at least 6 cycles of CHOP-like chemotherapy (median follow-up 8.4 years). Risk for chronic heart failure appeared markedly increased (SIR 5.4, 95% CI 4.1-6.9) with an AER of 208 excess cases per 10,000 person-years, whereas risk of coronary artery disease matched the general population (SIR 1.2, 95% CI; 0.8-1.8, AER 8/10,000 person-years). Risk of stroke was raised (SIR 1.8, 95% CI; 1.1-2.4, AER 15/10,000 person-years), especially if the neck was also irradiated to doses of more than 30-40 Gy.
On multivariate analysis, the same factors as described in **chapter 4**: pre-existent hypertension, smoking and salvage treatment increased the risk for all cardiovascular events. Old age was a risk factor for cardiovascular disease in **chapter 4**. However, in the person-years analysis, which corrected for morbidity risk by age in the general population, it appeared that this risk in elderly patients matched risk in the general population, while young patients were more at risk than other people of their age. The CMRN rates are not registered in such detail, that other factors as hypertension and smoking can be integrated in the analysis as for age and sex. Anyhow it is clear that life-style factors raise the risk of cardiovascular disease in both NHL patients and the normal population and therefore need attention during follow-up.
The impact of radiotherapy appeared to be dose-dependent. As more than half of the patients had received additional radiotherapy, several of them involving the mediastinum, more coronary and valvular disease was expected. However, only in the small subset of patients who had received 40 Gy or more, an increased risk of coronary disease was observed. As cardiotoxicity due to radiotherapy has been described as appearing late, more effect of additional radiotherapy may emerge after more prolonged follow-up.[41-44] Another explanation for the lack of observed radiotherapy-related cardiotoxicity after NHL treatment is already mentioned: radiotherapy techniques and fields have dramatically changed over the last decades. In earlier reports, mainly in Hodgkin's lymphoma patients, often high doses of radiotherapy (without chemotherapy) and extended fields have been given, techniques that nowadays will be addressed as outdated. [6, 7, 45, 46]

Reports on subclinical cardiomyopathy after doxorubicin-based chemotherapy in lymphoma patients show that cardiovascular changes are often present and can progress to clinical disease if not treated. If this ratio of chronic heart failure versus subclinical cardiomyopathy would be identical in the long-term follow-up of NHL patients, close monitoring of these patients would be mandatory. [47, 48] Given the fact that most cardiovascular events occurred already in the first years after NHL treatment (median interval around 3 years), follow-up of NHL patients in this period needs to be focused not only on recurrence of disease but on signs of cardiovascular damage as well. [49-52]

Second cancer has often been associated with NHL treatment, but few studies addressed risk according to specific treatments. In **chapter 6**, we estimated SIRs and AERs based on general population rates from the *European Network of Cancer Registries*. [53, 54] A total of 748 patients (aged 15-82 years) treated in the Netherlands, Belgium, France and Italy were analysed. All patients received fully-dosed CHOP-like chemotherapy, 65% received involved-field radiotherapy and 14% high dose treatment. Half of the patients needed salvage treatment and 37% were followed for >10 years. Cause of death was NHL in 79% of the patients; 4% died of second cancer (median survival 8.9 (0.8-20.5) years). Cumulative incidences (death by any cause as competing event) were 5% and 11% for solid cancer and 1% and 3% for AML/MDS at 10 and 15 years, respectively. Cancer risk appeared strongly age-related: in young patients high risks were observed for leukaemia (SIR 16.7, 95% CI 1.4-93.1, AER 5.0), Hodgkin's lymphoma (SIR 60.1, 95% CI 12.4-175.2, AER 15.7), colorectal (SIR 12.5, 95% CI 2.6-36.5, AER 14.7) and lung cancer (SIR 15.4; 95% CI 4.2-39.4, AER 19.8), while risk in patients older than 45 years matched the normal population. Cancer risk was significantly raised by smoking and salvage treatment. Only a minority of the patients received ASCT as part of first line or salvage treatment. Nevertheless, this treatment modality appeared a potential cancer risk factor in multivariate analysis, especially related to AML/MDS risk. Brown *et al*[55] described a cumulative 10-year second cancer incidence of 21% (median follow-up of 9.5 years) in a NHL cohort all treated with ASCT after conditioning with cyclophosphamide and total body irradiation. The second cancers observed consisted mainly of AML and MDS. In our cohort second haematological malignancies were also observed but to a far lesser extent than in this transplantation cohort, probably because of the fact that no total body irradiation had been given and that relatively low doses of cyclophosphamide had been used.[56] The 10-year solid cancer cumulative incidence rate given by Brown *et al* (with death as competing risk) in transplanted patients was 10%, but included non-melanoma skin cancers. In our cohort, the solid cancer risk of 4% increased up to 12% when skin cancer had been included. However, population-based skin cancer incidence rates are scarce and often unreliable, as these lesions are commonly removed without histology confirmation and therefore not registered. We left, therefore, non-melanoma skin cancer events out of the analyses. The same is held true for the diagnosis MDS, which is often based only on cytology, and is severely underscored in cancer registries, if at all present.

Interpretation and conclusions: As (R)-CHOP has become the world standard for aggressive NHL, the EORTC CHVmP/BV regimen has lost its significance, partly because

physicians feared excess toxicity by the supplementary drugs bleomycin and teniposide. In the update, the CHVmP/BV regimen appeared to be a very effective NHL treatment without high excess risk of leukaemia or lung toxicity having been observed. A future trial comparing the standards (R-CHOP vs. R-CHVmP/BV vs. R-ACVBP vs. R-CHOEP) among the different Lymphoma Groups would be very interesting to confirm the efficacy guided by IPI and modern (PET-guided) response criteria and moreover, to evaluate early and late toxicity of these complex regimens.

More than half of the patients treated with the CHvMP/BV for advanced aggressive NHL become long-term survivors. With additional anti-CD20 monoclonal antibody therapy the number of long-term survivors is expected to increase. As survival improves, late effects will become more and more relevant.
Long-term follow-up in 4 EORTC trials (1980-1999) shows that NHL survivors encounter problems as premature menopause, infertility, cardiovascular disease, disabling neuropathy, renal insufficiency and hypothyroidism. Doxorubicin and cyclophosphamide, the main drugs in NHL treatment appear to cause significant risk of chronic heart failure and second cancer (MDS/AML and bladder cancer).
Young female patients often encounter premature menopause, which seems partly to protect against breast cancer, but induces infertility, osteoporosis and higher risk of cardiovascular disease. Salvage treatment and smoking significantly raise risk of cardiovascular disease and second cancer even further.
The risk of late complications appeared to be strongly age-dependent; especially young patients (< 45 years) run into very high risk. Similarly, young patients are considered good candidates for more aggressive treatment approaches. In future trials, the marked high risk of congestive heart failure and second cancer, including leukaemia, should be, therefore, balanced against any preference for initial high-dose treatment.
Additional radiotherapy on the neck can induce hypothyroidism and stroke, and abdominal fields appeared to be related with secondary hypertension and renal insufficiency. The role of additional radiotherapy in risk of cardiovascular disease appeared to be dose dependent and minimal when doses of 30 Gy or less were given. The relatively small fields used did not increase risk of second cancer, but the numbers analysed were limited. Obviously, for estimation of the role of radiotherapy in late toxicity, data on techniques, dose, and field placement are mandatory and they significantly changed over time.

In conclusion, late toxicity in lymphoma treatment is often associated with radiotherapy. In the CHVmP/BV update, the role of additional radiotherapy appears to be, however, minimal and is clearly overruled by the number of serious late complications due to first line and second line chemotherapy for aggressive NHL. Therefore, when more therapy is needed, additional radiotherapy instead of more intensive chemotherapy should be seriously considered if late toxicity is taken into account.
All patients, but especially patients treated for NHL before the age of 45 years, need lifelong monitoring and should receive information on late consequences of treatment, focused on cardiovascular disease, premature menopause, renal failure and second cancer, including

MDS/AML risk. The treating physician needs to address the excess risk of smoking and overweight. Routinely check of blood pressure, lipid-profile and on indication bone mass, thyroid- and renal function during follow-up is recommended, as preventive care can reduce secondary morbidity and even mortality.

Fully dosed (within the consensus limits of 400 mg/m^2) doxorubicin-based chemotherapy for NHL appears to result in almost three excess cases per year of congestive heart failure per 100 patients followed. Equivalent risks can be expected when full dose doxorubicin-based chemotherapy is given in young patients for other cancer types, like breast cancer. More research in this field, based on long-term follow-up data and comparison to general population incidence rates is needed. As future trials become more and more equivalency trials, the high risk of second cancer and cardiac toxicity in young patients should be balanced against the potential survival benefit: more is not always better.

References

1. Raemaekers JM, Kluin-Nelemans JC, Teodorovic I, et al. The achievements of the EORTC Lymphoma Group. Eur J Cancer 2002, 38, S107-13 (suppl 4).
2. Fisher RI, Gaynor ER, Dahlberg S,et al.Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma.
3. N Engl J Med. 1993;328:1002-6.
4. Tumours of haematopoietic and lymphoid tissue: In Jaffe ES, Harris NL, Stein H, Vardiman JW, et al: World Health Organization Classification of Tumours. Lyon, France 2001: IARC Press
5. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-94
6. Shipp MA, Klatt MM, Yeap B, et al. Patterns of relapse in large-cell lymphoma patients with bulk disease: implications for the use of adjuvant radiation therapy. J Clin Oncol. 1989;7:613-8.
7. Girinsky T, Ghalibafian M.Radiation treatment in non Hodgkin's lymphomas: present and future directions. Cancer Radiother. 2005;9:422-6.
8. Yahalom J.Transformation in the use of radiation therapy of Hodgkin lymphoma: new concepts and indications lead to modern field design and are assisted by PET imaging and intensity modulated radiation therapy (IMRT). Eur J Haematol Suppl. 2005;66:90-7.
9. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545
10. Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on high-dose therapy with hematopoietic stem-cell transplantation in aggressive non-Hodgkin's lymphomas: report of the jury.Ann Oncol. 1999 ;1:13-9.
11. Blay J, Gomez F, Sebban C, et al. The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. Parma Group. Blood. 1998;92:3562-8.
12. Guglielmi C, Gomez F, Philip T, et al.Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial.J Clin Oncol. 1998;16:3264-9.
13. Friedberg JW, Neuberg D, Monson E, et al. The impact of external beam radiation therapy prior to autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma.Biol Blood Marrow Transplant. 2001;7:446-53.
14. Kahn ST, Flowers CR, Lechowicz MJ, et al.Refractory or relapsed Hodgkin's disease and non-Hodgkin's lymphoma: optimizing involved-field radiotherapy in transplant patients.Cancer J. 2005;11:425-31
15. Schöder H, Noy A, Gonen M, et al: Intensity of 18Flurorodeoxyglucose uptake in PET distinguishes between indolent and aggressive non-Hodgkin's lymphomas. J Clin Oncol 2005;23:4643-4651
16. Hoh CK, Glaspy J, Rosen P, et al: Whole-body FDG-PET for staging of Hodgkin's disease and lymphoma.

J Nucl Med 1997;38:343-348
17. Moog F, Bangerter M, Diederichs CG, et al: Lymphoma: Role of whole-body 2-deoxy-2 [F-18] fluoro-D-glucose (FDG) PET in nodal staging. Radiology 1997;203:795-800
18. Jerusalem G, Warland V, Najjar F, et al: Whole-body18F-FDG-PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. Nucl Med Commun 1999;20:13-20
19. Canellos GP: Residual mass in lymphoma may not be residual disease. J Clin Oncol 1988;6:931-933
20. Jerusalem G, Beguin Y, Fassotte MF, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999;94:429-433
21. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of positron emission tomography (PET) with fluorine 18 Fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: Is [18F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 2001;19:414-419
22. Juweid ME, Wiseman GA, Vose JM, et al: Response assessment of aggressive non-Hodgkin's lymphoma by Integrated International Workshop criteria and fluorine-18–fluorodeoxyglucose positron emission tomography. J Clin Oncol 2005;23:4652-4661
23. Jerusalem G, Beguin Y, Fassotte MF, et al: Early detection of relapse by whole-body emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol 2003;14:123-130
24. Römer W, Hanauske A-R, Ziegler S, et al: Positron emission tomography in non-Hodgkin's lymphoma: Assessment of chemotherapy with fluorodeoxyglucose. Blood 1998;91:4464-4471
25. Kostakoglu L, Coleman M, Leonard JP, et al: PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. J Nucl Med 2002;43:1018-1027
26. Spaepen K, Stroobants S, Dupont P, et al: Early staging positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose ([18F]FDG) predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;13:1356-1363
27. Mikhaeel NG, Hutchings M, Fields PA, et al FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol. 2005 Sep;16(9):1514-23
28. Hutchings M, Loft A, Hansen M, et alFDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107:52-9.
29. Allen-Auerbach M, Quon A, Weber WA, et al: Comparison between 2-deoxy-2-[(18)F}fluoro-D-glucose positron-emission tomography and positron-emission tomography/computed tomography hardware fusion for staging of patients with lymphoma. Mol Imaging Biol 2004;6:411-416
30. Haddy TB, Adde MA, McCalla J, et al: Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. J Clin Oncol.1998; 6:2070-9.
31. Andre M, Mounier N, Leleu X, et al: Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood 2004; 103:1222-8.
32. Aviles A, Diaz-Maqueo JC, Garcia EL,et al. Late lethal events in patients with diffuse large B cell lymphoma, a review of 714 patients treated in a single centre. Leuk Lymphoma 2001; 42:631-7.
33. Mudie N.Y, Swerdlow A.J, Higgins C.D, et al. Risk of secondary malignancy after Non-Hodgkin's Lymphoma: a British cohort study. J Clin Oncol 2006; 24:1-6
34. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc.1958; 53:457.
35. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1988; 16:1141-54.
36. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999 Mar 30;18(6):695-706.
37. Armitage JO, Carbone PP, Connors JM, et al. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21:897-906.

38. Van Leeuwen FE, Travis LB: Second cancers, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology. Philadelphia, PA, Lippincott Williams & Wilkins, 2005; 2575-2602.
39. van der Pal-de Bruin KM, Verkleij H, Jansen J, Bartelds A, Kromhout D. The incidence of suspected myocardial infarction in Dutch general practice in the period 1978-1994. Eur Heart J.1998; 19:429-434.
40. Lisdonk van de EH, Bosch van den WJHM, Huygen FJA, Lagro-Jansen ALM. Ziekten in de huisartspraktijk (3e druk). Maarssen: Elsevier/Bunge; 1999.
41. Gijssen R, Poos MJJM: Achtergronden en details bij cijfers uit huisartsenregistraties. Gezondheid en ziekte\ ziekte en aandoeningen\hartvaatstelsel\coronaire hartziekten. Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven, RIVM; 2003. http:www.rivm.nl/vtv/object_document/o3171nl7964.html.
42. Gustavsson A, Osterman B, Cavallin-Stahl E, et al: A systematic overview of radiation therapy effects in Hodgkin's lymphoma. Acta Oncol.2003; 42:589-604.
43. King V, Constine LS, Clark D, et al: Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys.1996; 36:881-9.
44. Glanzmann C, Kaufmann P, Jenni R, et al: Cardiac risk after mediastinal irradiation for Hodgkin's disease. Radiother Oncol.1998; 46:51-62.
45. Hull MC, Morris CG, Pepine CJ, et al: Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA.2003; 290:2831-7.
46. Zinzani PL, Gherlinzoni F, Piovaccari G, et al: Cardiac injury as late toxicity of mediastinal radiation therapy for Hodgkin's disease patients. Haematologica.1996; 81:132-7.
47. Constine LS, Schwartz RG, Savage DE, et al: Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. Int J Radiat Oncol Biol Phys.1997; 39:897-906.
48. Hequet O, Le QH, Moullet I, et al: Sub clinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol.2004; 22:1864-71.
49. Adams MJ, Lipsitz SR, Colan SD: Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol.2004; 22:3139-48.
50. Shan K, Lincoff AM, Young JB: Anthracycline-induced cardiotoxicity. Ann Intern Med.1996; 125:47-58.
51. Limat S, Demesmay K, Voillat L, et al: Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma. Ann Oncol.2003; 2:277-81.
52. Swain M, Whaley FS, Ewer MS: Congestive heart failure in patients treated with doxorubicin. Cancer.2003; 97:2869-79.
53. Steinherz LJ, Steinherz PG, Tan CT, et al: Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA.1991; 266:1672-7.
54. J.E. Tyczynski, E. Démaret, D.M. Parkin. Standards and Guidelines for Cancer Registration in Europe, IARC Technical Publication No. 40, IARC Press, 2003.
55. J.Ferlay, F. Bray, R. Sankila, D.M. Parkin. EUCAN: Cancer Incidence, Mortality and Prevalence in the European Union 1998, version 5.0. IARC Cancer Base No. 4. Lyon, IARC Press, 1999. Available from URL: http://www.encr.com.fr/encr.htm
56. Brown JR, Yeckes H, Friedberg JW, Neuberg D, Kim H, Nadler LM, Freedman AS. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol. 2005;23: 2208-14.
57. Travis LB, Curtis RE, Stovall M, Holowaty EJ, van Leeuwen FE, Glimelius B, et al. Risk of leukemia following treatment for non-Hodgkin's lymphoma. J Natl Cancer Inst. 1994;86: 1450-7.

Samenvatting

De term non-Hodgkin Lymfoom (NHL) omvat een heterogene groep lymfoproliferative maligniteiten, - in de volksmond lymfklierkanker genoemd - , met een biologie die varieert van milde vormen met een prognose van vele jaren, tot snel progressieve soorten, die indien onbehandeld, reeds fataal zijn in een paar weken. De diagnose NHL wordt door de patholoog gesteld met behulp van een weefselbiopt. De subtypering en pathologische classificatie van NHL is complex, geïllustreerd door verschillende voorgestelde, gebruikte en vervolgens weer vervangen classificatiesystemen. Behulpzaam is de praktische tweedeling tussen *indolente* (lage maligniteits graad) en *agressieve* (intermediair tot hooggradig) lymfomen, waarnaar de keuze van therapie, met inbegrip van chemo-, immuno- en radiotherapie kan worden bepaald.

In dit proefschrift worden patiënten met gevorderd agressief NHL beschreven. Meer dan de helft van deze patiënten is ouder dan 60 jaar. In 80% betreft het histologische subtype het diffuus grootcellig B-cel lymfoom. De prognose van iedere patiënt wordt naast het histologische type bepaald door de International Prognostic Index (IPI). Deze index is samengesteld uit een aantal eenvoudige parameters: de leeftijd van de patiënt, diens conditie, het serum LDH gehalte, het stadium van de ziekte en de aan- of afwezigheid van NHL lokalisaties buiten de lymfkliergebieden. De standaardbehandeling van gevorderd agressief NHL bestaat uit poly-chemotherapie, meestal in de vorm van 8 drie-wekelijkse CHOP-kuren, welke doxorubicin, cyclophosphamide, vincristine en prednison bevatten. Voor stadium I en II ziekte worden 3 kuren met aanvullende radiotherapie (30-40 Gy) gegeven, met uitstekende resultaten. Afhankelijk van de IPI bereikt circa 90% van de patiënten in zo'n vroeg stadium een complete remissie (CR) en is 80-90% nog in leven na 5 jaar. Toch, voor jonge, hoog risico stadium I en II patiënten wordt behandeling met 6-8 kuren bepleit. In het gevorderde stadium agressief NHL is de prognose veel somberder en zijn vele alternatieven voor CHOP geprobeerd: intensievere, hoge-dosis-chemotherapie schema's die, soms nog gevolgd worden door autologe stamceltransplantatie zijn gegeven om een betere overleving te bewerkstelligen. In *geen* van deze agressievere benaderingen bleek echter de extra toxiciteit op te wegen tegen een mogelijk overlevingsvoordeel. Met de introductie van hematopoëtische groeifactoren, is meer en meer mogelijk, zelfs bij bejaarde patiënten. Het was in deze groep patiënten dat de combinatie van chemotherapie met anti-CD20 monoklonale antilichamen (rituximab) superieur bleek aan chemotherapie alleen. Deze publicatie heeft de discussie over de meer agressieve benadering in het agressief NHL doen verstommen en R-CHOP is zeer snel tot nieuwe standaard verheven.

Al decennia lang worden patiënten met een NHL, waar mogelijk, in studieverband behandeld. In alle studies, zijn in- en exclusiecriteria vaak net (iets) anders. Voorts zijn de oudere studies ontworpen zonder IPI (1993), de WHO classificatie (1997) en respons criteria (1999). Hierdoor zijn studies moeilijk te vergelijken of te vertalen naar de dagelijkse praktijk. Aangezien CHOP-achtige schema's nu al bijna 30 jaar de standaardbehandeling van agressief NHL hebben gevormd, kunnen oude studies ons wel een goed beeld geven van de effectiviteit en de late schade van deze behandeling.

De EORTC (European Organization for Research and Treatment of Cancer) Lymfomen Groep coördineerde 4 opeenvolgende studies in patiënten met gevorderd agressief NHL tussen 1980 en 1999. In deze studies werd het CHOP-achtige schema CHVmP/BV (cyclophosphomide, doxorubicin, teniposide en prednisone met bleomycine en vincristine) als standaard gebruikt. In 2001 werd een update gestart en werd met extra vragenlijsten de eventuele late schade van de behandeling zo breed mogelijk geïnventariseerd. Van de in totaal 951 gerandomiseerde patiënten behaalden 63% een complete remissie (CR) met 8 kuren CHVmP/BV en 59% en 43% waren in leven na respectievelijk 5 en 10 jaar (mediane follow-up 8.7 (0.2-20.4) jaren). Opmerkelijk was dat de overleving na dezelfde CHVmP/BV chemotherapie duidelijk verbeterde over de tijd, ook na het corrigeren voor de retrospectief bepaalde IPI. Dit kon niet geheel verklaard worden door een verbetering van de 2^{e} lijnsbehandeling (introductie van de stamceltransplantatie) voor recidief of progressieve ziekte. Bias bleek verantwoordelijk: trapsgewijze correcties voor kleine verschillen in inclusiecriteria elimineerden het verschil in resultaat, vooral toen de histologiesubgroepen werden bestudeerd. Het systematische beschrijven van de analyse naar de effectiviteit van het CHVmP/BV schema in **hoofdstuk 2** onderstreept het risico van retrospectieve (subgroep)analyses en de bias die optreedt bij vergelijking van recente met oudere studies. Tijd en selectie zijn de meest prominente factoren die bias in lange termijnvergelijkingen veroorzaken. Door de veranderingen in het spectrum van patiënten toe te schrijven aan stadiummigratie, betere selectie, meer ondersteunende zorg, of veranderde verwijzingspatronen, zullen de meest recent behandelde patiënten bevoordeeld worden en kan een mogelijk voordeel van nieuwe behandelingen ernstig worden overdreven.

Tot de jaren ‘80 werd de meerderheid van patiënten met agressief NHL behandeld met radiotherapie. Na de introductie van poly-chemotherapie, zijn bestralingsvelden beperkt tot het ‘involved field’ principe, waarbij enkel de aangedane lymfklier- of orgaanregio wordt bestraald. Nadat de toevoeging van doxorubicine en introductie van CHOP de overlevingskansen sterk bleek te verbeteren zijn de radiotherapie indicaties gereduceerd naar initiële bulk, rest- of progressieve ziekte. Of het toevoegen van radiotherapie ter consolidatie in het geval van CR na 8 kuren nog nodig is, was onderwerp van de EORTC-studie 20932. De studie die de rol van deze z.g. ‘ijsberg’ bestraling gerandomiseerd uit zou zoeken, is helaas wegens gebrek aan aanbod van patiënten vroegtijdig gestopt. Dit schetst wel de huidige mening in Europa dat radiotherapie niet genoeg zal bijdragen aan de overleving terwijl men vreest voor meer toxiciteit.

Als na 8 kuren geen sprake is van een CR, is het belangrijk om vast te stellen hoeveel restziekte er nog is, en hoe deze het best behandeld kan worden. In **hoofdstuk 3** is beschreven dat patiënten in partiële remissie (PR) na 8 kuren een relatief gunstige prognose hebben, beter dan patiënten met progressieve of recidief ziekte. Dit pleit ervoor PR patiënten als afzonderlijke groep te zien en ook dusdanig te behandelen. De standaardbehandeling voor recidiverende agressieve NHL bestaat, indien de leeftijd en conditie van de patiënt dit toelaten, uit autologe stamceltransplantatie. Of deze agressieve benadering ook direct nodig is bij een PR na de eerste lijnstherapie is maar geheel de vraag. Als het geven van lokale radiotherapie

een PR kan omzetten naar een CR is dit een goed en veel minder toxisch alternatief. Buiten dat, kan er na te weinig respons op radiotherapie alsnog agressievere behandeling volgen. Omdat dit nooit gerandomiseerd is uitgezocht evalueerden wij alle 227 PR patiënten uit de EORTC studies. Van hen ontvingen 114 radiotherapie, 16 stamceltransplantatie, 93 tweede lijnschemotherapie en vier werden geopereerd. De mediane ziekte-vrije overleving was 4.2 jaar en 48% bleven de eerste 5 jaar in leven. De helft van de PR patiënten bereikten na deze behandeling een CR en de overleving was vergelijkbaar met patiënten direct in CR. De patiënten die behandeld waren met radiotherapie bleven langer ziektevrij en leefden significant langer in vergelijking met de andere behandelingen (voornamelijk chemotherapie). De overlevingswinst was het duidelijkst in patiënten met een IPI lager dan 3, met initiële bulk of zonder extranodale ziekte. In patiënten met een initiële IPI hoger dan 2 lijkt een meer agressieve benadering geboden, want geen van deze patiënten leefde langer dan 5 jaar. In de multivariate analyse met meenemen van prognostische factoren als o.a. stadium, bulk en het aantal lokalisaties van extranodale ziekte, bleek radiotherapie duidelijk de meest significante factor voor zowel ziektevrij blijven als overleven.
Deze retrospectieve analyse toont aan dat radiotherapie voor PR patiënten na volledig gedoseerde chemotherapie effectief kan zijn en beoordeling in een gerandomiseerd onderzoek (radiotherapie versus hoge-dosis-behandeling) is dan ook zeker gerechtvaardigd. Doch, om deze vraag te beantwoorden is een PET-scan geleid gerandomiseerd onderzoek met cross-over design nodig, dat slechts kan worden uitgevoerd wanneer verscheidene Lymfoomgroepen zo'n onderzoek samen zouden ondersteunen, gezien het beperkte aantal patiënten.

Aangezien het CHVmP/BV schema gedurende 20 jaar de EORTC-standaard is gebleven, gaf het EORTC-gegevensbestand een unieke mogelijkheid om late schade van dit schema en eventuele additionele behandelingen te onderzoeken. Van de 951 gerandomiseerde patiënten konden van 757 patiënten volledige gegevens over late schade verzameld worden, welke geselecteerd waren naar het feit dat zij tenminste 6 kuren chemotherapie hadden gekregen en meer dan een half jaar in de follow-up waren gebleven (mediane follow-up 9.4 (2.1-20.4) jaar). Er werden veel late niet-kwaadaardige complicaties (**hoofdstuk 4**) waargenomen, namelijk in 46% van de 757 patiënten. Na 15 jaar waren de cumulatieve incidenties (met dood door elke oorzaak als competing risk) van hart- en vaatziekten en vroegtijdige menopauze respectievelijk 20% en 29%. Nierinsufficiëntie (11%), hypertensie (8%) en invaliderende neuropathie (13%) werden ook frequent geobserveerd. Tweede lijnsbehandeling vormde een risicofactor voor de meeste late schade. Roken, leeftijd >50 jaar tijdens behandeling en preëxistente hypertensie waren de belangrijkste risicofactoren voor het ontwikkelen van hart- en vaatziekten. Bestraling, mits in dezelfde regio, verhoogde de kans op hypothyroïdie, longfibrose, hypertensie, gastro-intestinale complicaties en nierinsufficiëntie, maar niet op hart- en vaatziekten. Stamceltransplantatie, cisplatin en MOPP (mechlorethamine, vincristine, prednison en procarbazine) waren geassocieerd met infertiliteit en nierinsufficiëntie.

Hart- en vaatziekten vormden het grootse probleem bij patiënten na behandeling voor NHL, maar komen op die leeftijd ook zeer frequent voor in de algemene bevolking. Een

goede risico-inschatting vereist dan ook vergelijking met incidentie getallen van de normale bevolking. In **hoofdstuk 5** berekenden wij de standaard incidentie risico's (SIR) en de absolute extra risico's (AER) gebaseerd op algemene bevolkingsgetallen verzameld door de *continue morbiditeit registratie Nijmegen* in 476 (Nederlandse en Belgische) patiënten behandeld met minstens 6 kuren CHOP-achtige chemotherapie (mediane follow-up 8.4 jaar). Het risico voor chronisch hartfalen bleek duidelijk verhoogd (SIR 5.4, 95% CI 4.1-6.9) met een AER van 208 extra gevallen per 10.000 persoonsjaren follow-up, terwijl het risico van coronair lijden niet anders was dan in de algemene bevolking (SIR 1.2, 95% CI; 0.8-1.8, AER 8/10.000 persoonsjaren). De kans op CVA was ook verhoogd (SIR 1.8, 95% CI; 1.1-2.4, AER 15/10.000 persoonsjaren), vooral als tevens de hals was bestraald (> 40 Gy). In de multivariaat analyse kwamen dezelfde factoren als in hoofdstuk 4 worden beschreven naar voren: preëxistente hypertensie, roken en 2e lijnsbehandeling verhoogden significant de kans op het ontwikkelen van hart- en vaatziekten; het effect van radiotherapie bleek dosisafhankelijk te zijn.

Lymfoom behandeling is vaak geassocieerd met secundaire maligniteiten, maar weinig studies hebben het risico afgezet tegen specifieke behandelingen. Met behulp van incidentiecijfers uit de *European Network of Cancer Registries* zijn in **hoofdstuk 6** de SIRs en AERs berekend van secundaire tumoren in het NHL cohort. In totaal konden 748 patiënten (van 15-82 jaar) behandeld in Nederland, België, Frankrijk of Italië worden geanalyseerd. Allen waren behandeld met tenminste 6 kuren CHOP-achtige chemotherapie, 65% waren tevens bestraald en 14% had hoge-dosis-chemotherapie ontvangen. De helft van de patiënten was behandeld voor rest of recidief ziekte en 37% was langer gevolgd dan 10 jaar. Bij overlijden was in 79% van de gevallen NHL de oorzaak en in slechts 4% van de patiënten was een 2e tumor de reden (mediane overleving 8.9 (0.8-20.5) jaar). Cumulatieve incidenties (met dood door elke oorzaak als competing risk) [74, 75] waren 5% en 11% voor solide tumoren en 1% en 3% voor AML/MDS na respectievelijk 10 en 15 jaar. Het risico van secundaire maligniteiten bleek sterk leeftijdsafhankelijk te zijn. In jonge patiënten werden hoge risico's op leukemie (SIR 16.7, 95% CI 1.4-93.1, AER 5.0), Hodgkin lymfoom (SIR 60.1, 95% CI 12.4-175.2, AER 15.7), colorectale (SIR 12.5, 95% CI 2.6-36.5, AER 14.7) en long tumoren (SIR 15.4; 95% CI 4.2-39.4, AER 19.8) geobjectiveerd, terwijl het risico in patiënten ouder dan 45 jaar overeen kwam met dat van de normale bevolking. Roken en 2e lijnsbehandeling verhoogden significant het risico op 2e tumoren.

Bij het beschrijven van late schade is de gebruikte statistiek van groot belang. In een ziekte met een matige prognose of in oudere patiëntenpopulatie, kan een cumulatief risico berekend met de vaak gebruikte Kaplan-Meier model de incidentie sterk overschatten. Het is beter om de incidentie van late schade in dit soort patiëntenpopulaties te bepalen met een zgn. competing risk methode, welke corrigeert voor vroegtijdig overlijden voordat late schade zich kan ontwikkelen. Bij beschikbare nationale incidentie cijfers kan ook het risico t.o.v. de normale bevolking bepaald worden. Leeftijd, geslacht en leefomgeving cq. geografische regio beïnvloeden sterk dit soort risico's. Voorts veranderen nationale incidentiecijfers over de tijd. Persoonsjaren analysen per land en kalenderperiode vormen de beste manier om te

bepalen of het voorkomen van ziekte na behandeling, daadwerkelijk ook als late schade betiteld moet worden.

Interpretatie en conclusies: Met de standaardisering van (R-)CHOP wereldwijd is het CHVmP/BV schema voor gevorderd agressief NHL verlaten. Sommigen uiten bovendien de vrees dat er extra toxiciteit zou zijn door de toevoeging van bleomycine en tenoposide. Echter, in de update blijkt het EORTC schema in vergelijking met de standaard CHOP te resulteren in een effectieve behandeling zonder grote kans op longtoxiciteit of secundaire leukemie. Interessant zou zijn om in de toekomst de verschillende standaarden (R-CHOP vs. R-CHVmP/BV vs. R- ACVBP vs. R-CHOEP) van de verschillende Lymfoomgroepen te vergelijken in een equivalentie studie gericht op acute, maar ook late toxiciteit.
Meer dan de helft van de patiënten die met CHVmP/BV chemotherapie werden behandeld voor gevorderd agressief NHL overleeft ook op de lange termijn. Met de toevoeging van anti-CD20 monoklonale antilichamentherapie zullen waarschijnlijk nog meer mensen tot de lang overlevenden kunnen gaan behoren. Met de toegenomen overlevingskans na NHL, gaat late schade een steeds belangrijker rol spelen. Lange termijn follow-up in de 4 EORTC studies (1980-1999) laat zien dat de overlevenden problemen als vroegtijdige overgang, onvruchtbaarheid, hart- en vaatziekten, invaliderende neuropathie, nierfalen en hypothyroïdie tegenkomen. De belangrijkste componenten van de chemotherapie, te weten doxorubicine en cyclofosfamide, veroorzaken een duidelijk risico op chronisch hartfalen en in mindere mate op secundaire maligniteiten (leukemie and blaaskanker).
Het risico op late schade blijkt sterk leeftijdsafhankelijk te zijn, waarbij vooral de jonge patiënten (< 45 jaar) hoog risico lopen. Het zijn juist deze mensen die qua conditie in aanmerking komen voor agressievere behandelingsbenaderingen. De hoge risico's op hartschade en secundaire maligniteiten zullen echter in toekomstige studies, maar ook in de dagelijkse praktijk mee moeten wegen in de beslissing tot het daadwerkelijk standaardiseren van agressieve behandelmethoden.
Chemotherapie (vooral MOPP bevattende en consolidatie schema's voor stamceltransplantatie) brengt jonge vrouwelijke patiënten vaak vroegtijdig in de overgang, wat hen deels tegen borstkanker lijkt te beschermen, maar wel onvruchtbaarheid, osteoporose en hoog risico op hart- en vaatziekten kan veroorzaken. Roken en tweede lijnsbehandeling verhogen het risico op hart- en vaatlijden nog verder.
De rol van additionele radiotherapie in risico op hart- en vaatlijden bleek dosisafhankelijk en was minimaal als een dosis van 30 Gy of minder gegeven was. Met het gebruik van beperkte velden werd geen significant hoger risico op secundaire tumoren gevonden, doch de aantallen in deze analyses waren beperkt. Van groot belang in dit soort analyses is controle van de gegeven velden en verificatie van de organen of vaten die hierin hebben gelegen. Lage doses op de hals kunnen hypothyroïdie veroorzaken en abdominale velden lijken geassocieerd met hypertensie en nierinsufficiëntie. Stamceltransplantatie verhoogt duidelijk de kans op onvruchtbaarheid, nierinsufficiëntie en MDS/AML.
Al met al blijkt de late schade door de radiotherapie geïnduceerd bijna in het niet te vallen bij de kans op hart- en nierschade door de gegeven chemotherapie. Met de beperkte velden en moderne bestralingstechnieken blijkt de argumentatie om radiotherapie te verruilen voor

extra chemokuren omwille van de toxiciteit, dan ook ongegrond.
Alle NHL patiënten behoren langdurig nagecontroleerd te worden en uitleg te krijgen over late schade. Het is de taak van de behandelende arts de patiënt tijdens de follow-up te wijzen op het gevaar van roken en overgewicht. Tevens zal hij/zij routinematig de bloeddruk, het lipiden-profiel en op indicatie de botmassa, schildklier- en nierfuncties moeten (laten) controleren.
Volledig gedoseerde doxorubicine bevattende chemotherapie voor NHL blijkt te resulteren in bijna 3 extra gevallen van ernstig hartfalen op de honderd patiënten die per jaar gecontroleerd worden. Eenzelfde risico kan verwacht worden na doxorubicine bevattende chemotherapie die gegeven wordt in jonge patiënten voor andere soorten tumoren zoals b.v. borstkanker. Meer aandacht en onderzoek zijn nodig naar dit soort lange termijn effecten die niet alleen tot vroegtijdige morbiditeit maar ook tot mortaliteit kunnen leiden. Preventieve zorg kan deze morbiditeit verminderen en zelfs mortaliteit voorkomen.

Appendix

The names of the local investigators (with institutional affiliations, who entered more than 5 patients) are as follows: P. Carde (Institute Gustave Roussy, Villejuif, France; 126 patients); U.Tirelli. (Centro Di Riferimento Oncologico, Aviano, Italy: 124 patients); J. Baars (Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands; 94 patients); J.Thomas (U.Z. Gasthuisberg, Leuven, Belgium; 89patients); D. Bron (Institut Jules Bordet, Brussels, Belgium; 64 patients); J.C. Kluin-Nelemans (Leiden University Medical Center, Leiden, The Netherlands; 58 patients); W. Schroyens (Universitair Ziekenhuis Antwerpen, Antwerp, Belgium; 31 patients); K.J. Roozendaal (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; 29 patients); M. Monconduit (Centre Henri Becquerel, Rouen, France; 29 patients); J.M.M. Raemaekers (St. Radboud University Hospital, Nijmegen, The Netherlands; 27 patients); A.M. Pény (Centre Regional François Baclesse, Caen, France; 24 patients); C.M. Blanc (Hotel-Dieu de Paris, Paris, France; 24 patients); G.J. Creemers (Catherina Ziekenhuis, Eindhoven, The Netherlands; 21 patients); M.B. van 't Veer (Rotterdam Cancer Institute, Rotterdam, The Netherlands; 21 patients); W. Gerrits (Integraal Kankercentrum West, The Netherlands; 18 patients); G.J. Goverde (St. Ignatius Ziekenhuis, Breda., The Netherlands; 18 patients); A. van Hoof (A.Z. St. Jan, Brugge, Belgium; 16 patients); R. Debock (Algemeen Ziekenhuis Middelheim, Antwerp, Belgium; 14 patients); M. Fickers (Atrium Medisch Centrum, Heerlen, The Netherlands; 8 patients); G. Rosti (Ospedale Sta Maria Delle Croci, Ravenna, Italy; 8 patients); H.P. Muller (Streekziekenhuis Gooi-Noord, Blaricum, The Netherlands; 7 patients); H.C. Schouten (Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands; 7 patients); H.N.L.M. Bron (Maaslandziekenhuis, Sittard, The Netherlands; 7 patients); J.J. Keuning (St. Josef Ziekenhuis, Veldhoven, The Netherlands 7 patients); J. Michel (Centre Hospitalier de Tivoli, Louviere, Belgium; 6 patients): A.C. Tagnon (M.C. De Tournai, Tournai, Belgium; 6 patients).

Curriculum Vitae

Elizabeth Charlotte Moser was born on March 26, 1973 in Amsterdam. She passed her secondary school exam (Athenaeum-B) in 1991 at the 'Rijks Scholen Gemeenschap' in Heerenveen. After one year of training as radiographer in Haarlem, she decided to start medical training at the Free University of Amsterdam. She performed research at the Departments of Internal Medicine (Dr. J.J.J. de Sonneville) and Gynaecology at the Free University of Amsterdam and Stellenbosch University in Cape-Town, South Africa (Prof. Dr. H.J. Odendaal). In 1998 she obtained her medical degree (Cum Laude) and started working at the Department of Gynaecology of the Leiden University Medical Centre (Prof. Dr. J.B.M.Z. Trimbos). Because of her special interest in oncology, she decided in 1999 to initiate her carrier in radiotherapy at the Amsterdam Medical Centre (Prof. Dr. D. Gonzalez Gonzalez), and she officially started her specialist training in Radiation Oncology at the Leiden University Medical Centre in 2001 (Prof. Dr. E.M. Noordijk). In between, she went for a fellow-ship (financed by the Dutch Cancer Society) to the EORTC (European Organization for Research and Treatment of Cancer) Data Centre in Brussels, Belgium in 2002 and worked on the update of the 4 EORTC-trials, the basis of this thesis. She received 'The ASCO Merit Award' for her first presentation of results in 2003 (chapter 2), just after returning to Leiden to continue her specialist education. In 2005, she received the 'Jan van Steenbergen prijs' for her later presentations on late effects of NHL treatment (chapter 5). In June 2006 she finished her training as Radiation Oncologist. She started working at the Department of Radiotherapy of the Brest University Hospital, France, in October 2006. She is married and has two children (Loïc and Margot).

Publications

Moser EC, Noordijk EM, van Leeuwen FE, Baars JW, Thomas J, Carde P, Meerwaldt JH, van Glabbeke MMB, Kluin-Nelemans JC. Risk of secondary cancer after aggressive non-Hodgkin's lymphoma; an EORTC cohort study. Haematologica 2006; 11, November

Moser EC, Kluin-Nelemans JC, Carde P, Meerwaldt JH, van Glabbeke MMB, Noordijk EM. Impact of Involved field radiotherapy in partial response after doxorubicin-based chemotherapy for advanced aggressive non-Hodgkin's lymphoma. *Int J of Radiat Oncol Biol Phys, 2006 Aug.1*

Moser EC, Kluin-Nelemans JC and Noordijk EM. Radiotherapie bij restziekte van agressief non-hodgkin lymfoom. *Nederlands Tijdschrift voor Hematologie, 2006 October*

Moser EC, van Leeuwen FE, Noordijk EM, le Sessie S, Baars JW, Thomas J, Carde P, Meerwaldt JH, van Glabbeke M, Kluin-Nelemans JC. Relative risk of cardiovascular disease after treatment for aggressive Non-Hodgkin's lymphoma compared to the Dutch population. *Blood* 2006;107:2912-19.

Moser EC, Noordijk EM, Carde P, Tirelli U, Baars JW, Thomas J, Bron D, Meerwaldt JH, van Glabbeke MMB, Raemaekers JMM, Kluin-Nelemans JC. Late non-neoplastic complications in aggressive non Hodgkin's lymphoma patients across four randomized EORTC-trials. *Clin.Lymphoma Myeloma* 2005;20;1-9.

Wiggenraad R, Flierman L, Moser EC. Prophylactic gastrostomy placement and early tube feeding limit weight loss during chemoradiation for advanced head and neck cancer. *Radiother Oncol* 2004;64:S312-S313.

Moser EC, Noordijk EM, van Glabbeke M, Teodorovic I, de Wolf-Peeters C, Carde P, Baars JW, Tirelli U, Raemaekers JMM, Kluin-Nelemans JC. Long term efficacy of the CHVmP/BV regimen used for aggressive non Hodgkin's lymphoma across three randomized EORTC-trials *Eur. J. Cancer* 2004;40:474-80.

Stalpers LJA, Moser EC. Results of Radiotherapy for drooling in amyotrophic lateral sclerosis. *Neurology* 2002;58:1308.

Moser EC, van den Berk GEL, Odendaal HJ, Smith M. Nucleated red blood cells in foetuses delivered for early onset severe pre-eclampsia. *Int. J. Gynaecol. Obstet* 1999;64:183-185.

Moser EC, van den Berk GEL, Smith M, Odendaal HJ. Liver, renal and platelet counts after delivery in patients with severe pre-eclampsia. *S.Afr.Med. J.* 1998;88:1595-96.

Seubert M, de Sonneville JJJ, Moser EC, Seissler J, Heine RJ. Prevalence and predictive value of GAD- and IA-2-antibodies in Diabetes Mellitus diagnosed above 40 years of age. *Diabetalogica* 1996;39:Sl

Nawoord

Onderzoek doe je niet alleen en ik wil dit boekje dan ook graag afsluiten met het bedanken van alle mensen binnen de EORTC Lymfomen Groep, de afdeling klinische oncologie in het LUMC en het EORTC datacentrum in Brussel voor het enthousiasme en de mogelijkheden om het project daadwerkelijk af te ronden. Het zijn de coauteurs geweest die mij met menig taal- en datageworstel naar het eindresultaat hebben geleid en hen zou ik expliciet wil bedanken. Hanneke, zonder jou was dit project er überhaupt niet geweest en vervolgens veranderde jij elke bladzijde in een leermoment: dank je wel voor al je geduld en medeleven.

Toen ik bij het project van de EORTC-update betrokken raakte en vervolgens in Brussel terecht kwam, overleed een goede vriendin. Als kind was zij behandeld voor kanker en vanaf die tijd droeg zij moedig hiervan de gevolgen en littekens. Zoals zij zelf zei had de behandeling van destijds haar toch 30 jaar leven opgeleverd, terwijl ik met name de minstens 30 zag die nog hadden moeten volgen. Door uitgebreide vaatschade als gevolg van bestraling raakte eerst haar nier en later darmen dusdanig beschadigd dat zij uiteindelijk is overleden. Zij was uniek, maar hierin helaas niet alleen.
In de dagelijkse oncologiepraktijk zetten wij vaak alles op alles curatie te bereiken en juist bij jonge mensen gaan we hierin heel ver. Als dit vervolgens lukt en de kanker is overwonnen, blijkt er echter een heel nieuwe strijd te ontstaan. Onderzoek is nodig om ook hier onze verantwoordelijkheid te kunnen nemen en deze mensen bij te staan.

Verder is ‘mantelzorg’ in de vorm van vrienden en familie voor dokters van even groot belang als voor patiënten, zij het niet groter, zeker als zij proberen naast klinisch werk ook nog wetenschappelijk bezig te zijn; lieve mensen, dank voor alle steun.