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Fatigue in cancer treatment - assessment, course and etiology

Avhandling for graden doctor medicinae

Trondheim, juni 2007

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ISBN ISBN 978-82-471-3022-3 (trykt utg.)
ISBN ISBN 978-82-471-3036-0 (elektr utg.)
ISSN 1503-8181

Avhandlinger ved NTNU, 2007:138

Trykt av Tapir Uttrykk

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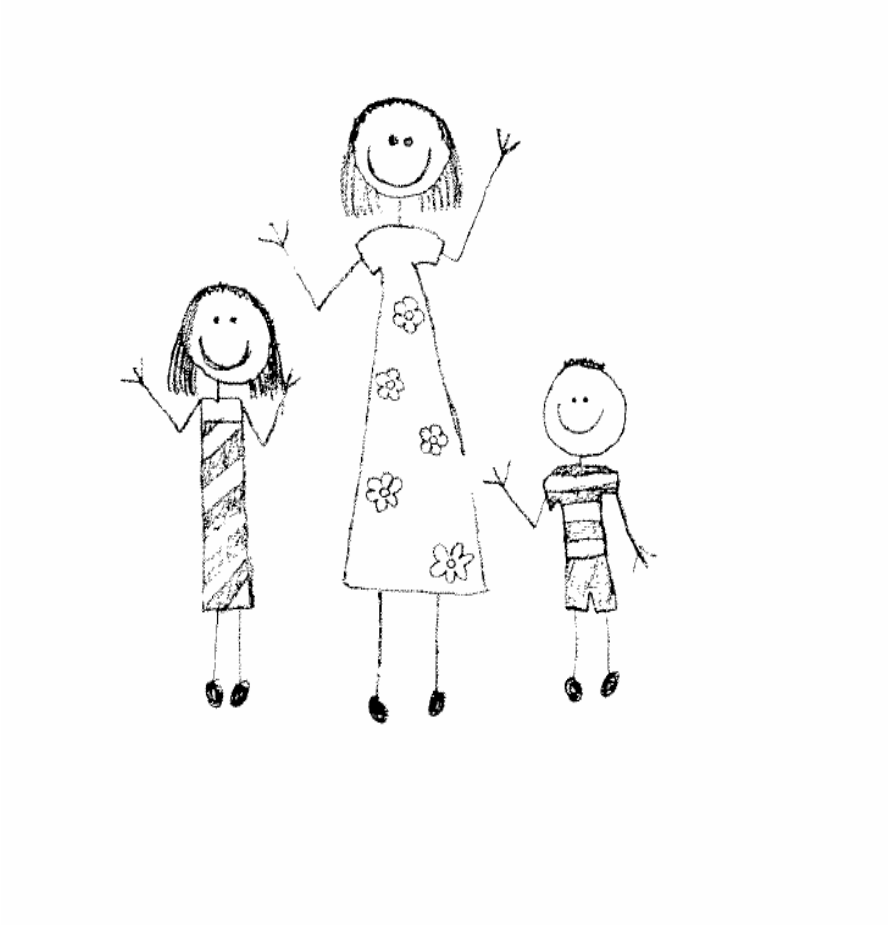


To Emilie and Peder August

Abstract

Aims. The major aims of the present work were to increase the understanding of cancer related fatigue with respect to assessment methodology, frequency and possible etiology. The validity of two fatigue instruments was evaluated and compared in order to enable an evaluation of the fatigue assessments in different patient cohorts. Secondly, the frequency and course of fatigue during curative cancer treatment, as well as the frequency of fatigue in cancer survivors were investigated in order to demonstrate the symptom burden during treatment and after ending curative treatment. The tertiary aim was to explore possible etiologic factors that may explain fatigue in cancer survivors.

Background: The long term survival of cancer patients has risen dramatically during the last decades. Several follow-up studies have shown that the long term side effects of curative treatment are more pronounced than first expected. During the last years much more attention have been given to the need for systematic follow up and assessment of long term effects on objective and subjective health after curative treatment. Fatigue is reported to be one of the most frequent and disturbing symptom in cancer patients in general, and is experienced by cancer patients at all stages of their disease. Fatigue is also observed as a subjective late effect in cancer survivors. The prevalence of chronic fatigue (elevated fatigue levels > 6 months) is 2-3 times higher in Hodgkin´s Disease Survivors (HDS) than in the general population. Despite the high prevalence of fatigue, the etiology and causes of the symptom is not clear. Most studies of fatigue in cancer patients are cross sectional and of limited value when exploring the frequency and contributing factors to the etiology. Since fatigue is a subjective phenomenon, it is agreed that it should be measured by patients self assessment. Several instruments are developed for fatigue measurement, both uni - and multi - dimensional. As in research in general, the validity of the subjective outcomes are of crucial importance.

Methods: Five different studies were conducted in order to meet the major aims. Two aspects of the validity of the fatigue scale in the health related quality of life (HRQoL) questionnaire EORTC QLQ-C30 were addressed, the dimensionality of the fatigue scale (FA) and the sensitivity of the FA. The instruments were evaluated in two different patient cohorts, a palliative patients cohort and a cohort of hematooncological malignancy patients after

curative treatment. A longitudinal follow up study of HRQoL and fatigue in lymphoma and leukaemia patient before, during and until three to five years post treatment with high dose chemotherapy and stem cell support was conducted in order to evaluate the trajectory of fatigue and HRQoL during and after treatment, and to compare symptom and function levels between the cohorts. The relationship between fatigue and late effects of pulmonary, cardiac and endocrine function as well as brain MRI abnormalities were investigated in order to explore possible etiologic factors of fatigue in lymphoma survivors after transplant therapy and in HDS after standard treatment.

Findings: The EORTC QLQ-C30 fatigue scale is one - dimensional measuring physical fatigue. A floor/ceiling effect illustrated a poor sensitivity of the scale in patients with lowest respectively highest fatigue level. According to the longitudinal study lymphoma patients report more fatigue, poorer functioning and poorer quality of life as compared to leukaemia patients three to five years after post transplant and as compared to the general population. This pattern was also observed at baseline before transplant. Pulmonary dysfunction was associated with fatigue in HDS whereas cardiac and thyroid dysfunction as late effects after curative treatment did not explain high levels of fatigue in HDS. A questionable association between fatigue and thyroid and gonadal dysfunction were observed. Neither cytokines nor brain white matter lesions were associated with fatigue in HDS.

Conclusion: The fatigue subscale, FA, of the EORTC QLQ C30 is measuring physical fatigue. The ability of FA to discriminate between patients with different levels of fatigue is poorer as compared to a fatigue specific instrument (Fatigue Questionnaire). The validation of instruments in different cohorts with differences in frequency and intensity of symptoms is important.
As illustrated in earlier studies, fatigue is a prevalent symptom in lymphoma patients before and after treatment indicating that fatigue may be related to the lymphoma disease.
Pulmonary late effects was predictor of fatigue in HDS, and the explanatory value of cardiac and endocrine late effects need further investigation. Follow-up program that extend 15-20 years post treatment should be considered in order to explore the effect of clinical relevant medical late effects on subjective health including fatigue.

Table of content

Acknowledgements

The present thesis was carried out at the Institute of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, NTNU, and the Department of Oncology, St. Olavs Hospital, Trondheim University Hospital.

I wish to express my sincere thanks to my main supervisor Professor Stein Kaasa for introducing me to clinical research. I was introduced for his research group when I startet as a junior registar at the Department of Oncology in 1997. The enthusiastic and scientifically highly qualified milieu in the research group that later was called “Pain and Palliation Research Group” made it easy to go on as a research fellow. It has been a privilege to be a part of the collegium. I will thank Professor Stein Kaasa for sharing his extensive experience within clinical research, and for his supervision, continuous support and encouragement.

I thank my co-supervisor Professor Jon Håvard Loge for his creativity, knowledgeable guidance and support, and for not loosing enthusiasme and belief in me in finishing this work. I appreciate your “palliative” telephone calls!

I acknowledge the pharmaceutical company Janssen-Cilag AS for an unrestricted grant for a three years research fellowship.

Dr.phil.Marianne Jensen Hjermstad and co-author enabled the follow-up study, for which I am very thankful. I thank Dr. Peter Fayers for co-authorship, his expert statistically guidance and advices. I thank the “lymphoma group” at the Norwegian Radium Hospital for giving me access to their unique patient material and for their co-authorships. Dr.med Tone Nordøy, Tromsø University Hospital, and Dr.med. Mai Brit Lund and Professor Kolbjørn Forfang, National Hospital, enabled through their research the ability for me to connect somatic late effects and subjective health within lymphoma survivors. I am very thankful for giving me the opportunity to explore this research field.

Elisabeth Brenne, Pallliative Medicine Unit, Department of Oncology, St Olavs Hospital was a close collaborator for the prospective study of palliative care patients.

I am grateful that Research Group was my main place of work during the periods as a research fellow, and it is still my “second home”. I thank the Group for providing me very good facilities and working conditions. Especially I want to thank Gunn-Heidi Tobekk, Elin Steen, Karin Tulluan, Finn Gutvik and Berit Bjelkåsen for the technical and secretarial support whenever I needed, and all the colleagues for their contribution to the social and scientific milieu.

I returned as a senior registar at the Department of Oncology after finishing the scholarship periode. I will thank the head of department, Dr.med Helge Haarstad, for giving me the opportunity to finish this thesis parallell to the clinical work. I thank all good colleagues for their support. Especially, I wish to thank Ragnar Telhaug and Unn Merete Fagerli for their tolerance and patiency during the final work of this thesis. I want to thank my colleagues and friends Jo Åsmund Lund, Arne Solberg, Anne Kvikstad and Monica Eidem for professional and personal support, good discussions and advices.

I attended the mentor program for female researchers at the NTNU as an adept in 2003. The will thank my enthusiastic mentor, Prof. Asgeir J.Sørensen at the Department of Marine Technology for professional and inspiring meetings. In spite of the professional distance between marine cybernetics and life-threatening diseases, our reflecting and in-depth discussions showed that the gap was nevertheless minimal.

My research fellow and co-author Line Oldervoll have introduced me to the science of physical interventions, and I am looking forward to continue our collaboration.
Thanks to colleague and friends Anna Catharina Hegstad and Lars Johan Materstvedt for interesting and enthusiastic philosofic discussions accompanying evening meals. I address special thanks to Frode, I am deeply grateful for your encouragement and support, and for your warmth and sincere friendship.

I want to express my sincerest gratitude to my family: To my parents Berit and Jan for your love, for your encouragement and support in all my choices, and for never ending helping me with practical assistance or in taking care of the children. You take a great part in this thesis. My sister with family for support and for magic moments in the mountains sharing the interest in hill walking. To Dag for your tolerance, our close friendship, and your devotion to our wonderful children.

Finally, my greatest thoughts I give my children Emilie and Peder August, for your love and inspiration, for your patiency through all these years, and for all the joy you bring me. I am so proud of you.

Trondheim, Mars 2007

Heidi Knobel

List of papers

The thesis is based in the following publications, which are referred to in the text by Roman numeral I-V

I. **Knobel H, Loge JH, Brenne E, Fayers P, Hjermstad MJ, Kaasa S. The validity of EORTC QLQ-C30 fatigue scale in advanced cancer patients and cancer survivors.** ***Pall Med 2003; 17: 664-672***

II. **Hjermstad MJ, Knobel H, Fayers P, Loge JH, Holte H, Brinch L, Kaasa S. A 3-5 years prospective study of health related quality of life, fatigue, anxiety and depression after stem cell transplantation.** ***Bone Marrow Transplant 2004; 34: 257-266***

III. **Knobel H, Loge JH, Nordhøy T, Kolstad AL, Espevik T, Kvaløy S, Kaasa S. High level of fatigue in lymphoma patients treated with high dose therapy.** ***J Pain Symptom Management 2000;19 (6): 446-456***

IV. **Knobel H, Loge JH, Lund MB, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors.** ***J Clin Oncol 2001;19: 3226-33***

V. **Knobel H, Loge JH, Kvistad KA, Klepstad P, Telhaug R, Kaasa S. Brain lesions in chronic fatigued survivors of Hodgkin´s Lymphoma-an explorative study.** ***Submitted European Journal of Cancer***

List of abbreviations

ABMT	= Autologous bone marrow transplantation
ASCT	= Autologous stem cell transplantation
BMT	= Bone marrow transplantation
CAD	= Coronary artery diseases
COPD	= Chronic obstructive pulmonary disease
EBV	= Epstein Barr Virus
EORTC QLQ-C30	= The European Organisation for Research and Treatment Core Questionnaire
FQ	= Fatigue Questionnaire
FSH	= Follicular-stimulating hormone
Gy	= Gray
HADS	= Hospital Anxiety and Depression Scale
Hb	= Haemoglobin
HD	= Hodgkin´s Disease
HDC	= High dose chemotherapy
HDS	= Hodgkin´s Disease Survivors
HPA	= Hypothalamic-pituitary-adrenal axis
HRQoL	= Health related quality of life
KPS	= Karnofsky Performance Status
LH	= Luteinizing hormone
NHL	= Non-Hodgkin´s Lymphoma
NRH	= Norwegian Radium Hospital
MF	= Mental fatigue
MRI	= Magnetic resonance imaging
NH	= National Hospital
PF	= Physical fatigue
QoL	= Quality of life
SCT	= Allogenic stem cell transplantation
TF	= Total fatigue
TBI	= Total body irradiation
TLCO	= Transfer factor for carbon monoxide
WHO	= World Health Organization

“Nothing in life is to be feared. It is only to be understood.”

Madame Curie

Introduction

Preface

In Norway 24, 434 new cases of cancer were reported in 2004, 12, 919 in men and 11,515 in women, and approximately 50% are expected to be cured from the disease.[1] The most common treatment modalities are surgery, chemotherapy and radiotherapy, often in combination depending upon the primary diagnosis, stage of the disease and other prognostic factors.

The prognosis for survival from cancer has steadily improved since the 1950s with a 5-year relative survival increasing from 25% to 50% in men, and from 37% to 58% in women. The improved prognosis is most pronounced in certain malignancies such as Hodgkin´s Disease (HD), testicular cancer and childhood cancers, with less pronounced improvement for the most common types of cancers such as breast, lung, prostate and gastrointestinal cancers.

By the improved prognosis and increasing number of survivors, studies of late effects have become more important. Late effects can mainly be divided into three categories. Firstly, there are the late somatic effects that include secondary cancers or affections of one or more organ systems. Secondly, there are the late effects of subjective nature, which include symptoms such as fatigue, pain and psychological phenomena. Thirdly, there are the late effects that may be categorized within the social domain which encounter difficulties in returning to normal life such as resuming work, difficulties in partnership or in participation in leisure activities.

In general, late effects are more prevalent, serious and persistent than expected [2]. Furthermore, how to rehabilitate and/or treat the survivors suffering from late effects lack systematic and adequate documentation.[2] An essential issue which is hardly discussed in the literature is whether and how somatic late effects influence on the subjective health of cancer survivors.

Quality of life (QoL) reflects the definition of health as proposed by the World Health Organization (WHO) in 1947 with emphasis on the subjective aspect of health and not only the absence of disease.[3] During the 1980's and 1990's the concept of QoL became more directed towards health by the introduction of the term Health-Related Quality of Life (HRQoL). The latter operationalizes health as encompassing a social, a physical and a mental dimension.

HRQoL can be regarded as a narrowing of the concept QoL, and some therefore prefer the term subjective health. QoL as a health-related construct is recognized as a primary endpoint in the palliative phase of cancers, as a secondary endpoint in life-prolonging oncological treatment and is relevant for assessment of toxicity and side-effects in curative oncological treatment. Among cancer survivors, HRQoL captures the subjectively experienced consequences of cancer survivorship.

Fatigue is of subjective nature and therefore recognized as one domain within the HRQoL-concept. Fatigue is reported to be one of the most frequent and disturbing symptom in cancer patients in general, and our present knowledge of its prevalence indicates that fatigue is experienced by cancer patients at all stages of their diseases. Fatigue is also commonly observed as a subjective late effect in cancer survivors, and the prevalence of chronic fatigue is nearly three times higher in Hodgkin´s Disease survivors (HDS) than in the general population.[4] Despite the frequency of fatigue and the increasing numbers of publications on cancer-related fatigue during the last decades, the etiology behind fatigue in general and cancer-related fatigue in particular is poorly understood. Further, most published studies on cancer-related fatigue have been cross-sectional and therefore of limited value in studying contributing factors and deciding which patients are in need of specific interventions.

In order to prevent, treat, rehabilitate and/or support fatigued cancer patients, a better understanding of how fatigue develops over time and identification of underlying etiology is therefore warranted.

Lymphomas

The term “malignant lymphoma” was originally introduced by Billroth to describe neoplasm of lymphoid tissue.[5] Lymphomas are traditionally divided into Hodgkin´s Disease (HD) and Non-Hodgkin´s Lymphoma (NHL) due to differences in histology and clinical course. Due to the recent improvement in the diagnostic of lymphomas, the name Hodgkin´s Disease is internationally mainly replaced with Hodgkin´s Lymphoma. However, since the patients described in this thesis were treated several years ago according to the current name Hodgkin´s Disease, the diagnosis in this thesis is designated Hodgkin´s Disease (HD).

Hodgkin´s Disease

Hodgkin´s Disease (HD) was first described in 1832 as a relatively uncommon malignancy.[6] It is characterized by the presence of Sternberg-Reed cells, which are multinucleated giant cells surrounded by a variety of reactive bystander cells such as lymphocytes, macrophages, neutrophils, histocytes and plasma cells. As late as in 1940, HD was classified as an infectious disease.[7] Epstein-Barr virus (EBV) may play a role in the pathogenesis of HD, and is subject of intense research. Thus, chronic viral infections as well as activation of cellular oncogenes, loss of tumour suppressor genes and the deregulators of several cytokines might be factors involved in the pathogenesis of HD.[8] HD exists in two entities, classic HD (95% of the cases) and nodular lymphocytic predominance (paragranulome; 5% of the cases). The subgroups of classic HD are nodular sclerosis (45% of the cases), mixed cellularity (40%), lymphocytic predominance (5%) and lymphocytic depletion (5%).

In year 2004, 120 new cases of HD were diagnosed in Norway. The incidence rates have been stable or decreased slightly over time (Fig.1).[1] There is a bimodal age distribution, indicating that nearly 30% of new cases are found among subjects aged 20-29 years. The second peak is found among subjects 60 years or older (Fig.1).[9] Approximately 1800 Norwegians are alive after curative treatment of HD.[1]

Hodgkin lymphoma

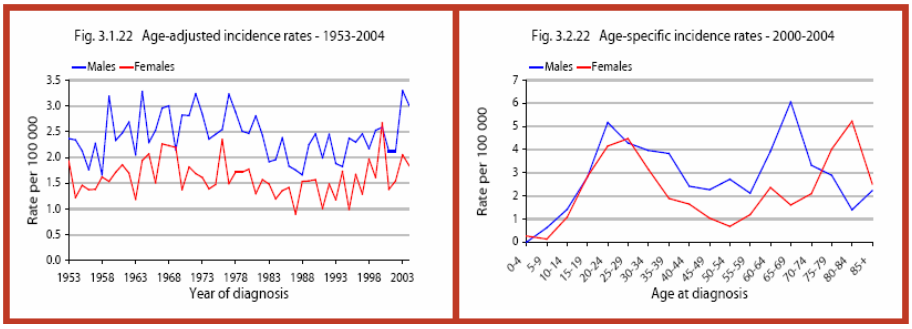


Fig. 1. Incidence of Hodgkin´s Disease [1]

HD primarily affects lymph nodes. Most patients develop enlarged lymph nodes in the cervical region (60%), the axillar regions, and the inguinal regions or in the abdomen. In advanced stages, the disease spreads to the spleen, bone marrow, liver or lung. A system for clinical staging of the disease was launched in 1960 (The Rye Classification),[10] and modified in 1970 (Ann Arbor Staging System.[11] The classification is based upon the spread to lymph node regions, to extralymphatic organs and whether the disease is located to one or both sides of the diaphragm (Table 1). Staging into sub stage A or B is based upon the absence (A) or presence (B) of one or more constitutional symptoms; fever, night sweat and weight loss >10% during the last 6 months. This staging system has been used throughout this thesis, and is available for both HD and for NHL.

Table 1. Ann Arbor Staging System for Hodgkin's Disease and Non Hodgkin´s Lymphoma

Stage	Criteria
I	Involvement of single lymph node region (I) or of single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on same side of the diaphragma alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
III	Involvement of lymph node regions on both side of diaphragma (III), which may include splen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES).
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without lymphatic involvement.

All cases are subclassified to indicate the absence (A) or the presence (B) of the systematic symptoms of significant fever, night sweats or unexplained weight loss exceeding 10% of normal body weight.

Treatment and prognosis

During the last three decades, as a result of advances in staging techniques and the successful development of effective therapeutic regimens, HD, a previously fatal malignancy, has become highly curable. The 5 years relative survival rate is approximately 75% for all cases. The age at diagnosis is a highly significant prognostic factor, with improved survival rate for patients younger than 65 years of age at time of diagnosis.

The treatment principles for HD in Norway have been relatively unchanged during the last 15 years. Stage I or II above diaphragm is most frequent, and patients without risk factors (unfavourable prognostic variables) have until recently been treated with radiotherapy alone (most often mantle field). Today, chemotherapy is standard combined with radiotherapy. Patients with risk factors have been and still are treated with combined chemotherapy and radiotherapy.

Treatment of stage III and IV basically include chemotherapy, eventually added by radiotherapy similar to those without risk factors.

Radiotherapy

In the 1960s, the use of high-dose fractionated large-field irradiation provided the first high cure rates for patients with limited disease.[12] Based upon knowledge of patterns of spread of the disease, the radiotherapy was divided into two major volumes: 1) The mantle field including the lymph nodes of the neck, axillae and mediastinum, and 2) The inverted Y-field including the paraaortic and pelvic area. A continuous revision of the radiotherapy techniques and better knowledge of response and radiotherapy-related toxicity, have lead to further refinements of fields and dosages. Today the field definitions are more functional, and the following fields are standard: 1) Involved field, which include the involved lymph nodes and the other lymph nodes within the same lymph node region and 2) Extended field, which include involved field as well as the adjacent lymph node regions. The latest within radiotherapy is the involved node field, which include the affected lymph node only. Fractional doses of 2,0 Gray (Gy) (from 1980 until mid 1984) or 1,8 Gy (from 1984 and onwards) given 5 days a week to a mean total dose of 40,6 Gy (range 40-42) have been standard. Today the standard radiation dose for HD is 1,75 Gy to a total dose of 29,75 Gy. The patients included in this thesis have mainly been treated according to the standard treatment regimen in 1970`s and 1980`s (2 Gy, alternatively 1,8 Gy).

Chemotherapy

The introduction of combination chemotherapy was the second important step to improve the survival rates of HD. In 1964 investigators at the National Cancer Institute developed a four-drug combination chemotherapy program, MOPP (vincristine, procarbazine, mustine, and prednisone). This landmark study established the curability of more than 50% of patients with stage III and IV, and was since then the gold standard for the treatment of advanced disease.[13] The acute side effects of MOPP, primarily gastrointestinal and neurological toxicity, required investigation of alternative regimens with the desire to obtain equivalent or improved results with less toxicity. Alternative regimens have been COPP replacing mustine by cyclophosphamid, or ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone). Since late 1970s the ABDV – regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) has gained an important position in the treatment of HD. The ABDV-regimen has documented improved effectiveness and less toxicity as compared to the MOPP-regimen.[14] The ABVD is the standard regimen today (two or four

cycles), in case of insufficient response/progression, BEACOPP (cyclophosphamid, doxorubicin, etoposid, procarbazin, prednisone, vincristine, bleomycin) is the treatment of choice. For patients above 60 years, the CHOP-regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) and radiotherapy is standard. Details to the treatment regimens are given in the national treatment protocol (*Nasjonale handlingsplan for maligne lymfomer; 2003, revised in 2004 and 2006).*

Non-Hodgkin´s Lymphoma

The Non-Hodgkin´s Lymphomas (NHL) constitute a heterogeneous group of malignant neoplasma arising from B-and T-lymphocytes. The histological subtypes are numerous, the localization in extra nodal tissues, its capacity to remain localized or to disseminate throughout the body make this malignancy less predictable than HD.

NHL is more prevalent than HD. In Norway more than 700 new cases of NHL are diagnosed annually.[1] The incidence of NHL is steadily increasing in all countries, and the incidence among men is higher as compared to women (Fig.2). Dramatic changes and improvements with the diagnostic of lymphomas in general and changes in the classification of HD and NHL have had an impact on the changing trends. New improvements within immunology and cytogenetic/DNA-technology and in particular the use of immunphenotyping in the diagnostic have improved the classification system and ensured a correct diagnosis.

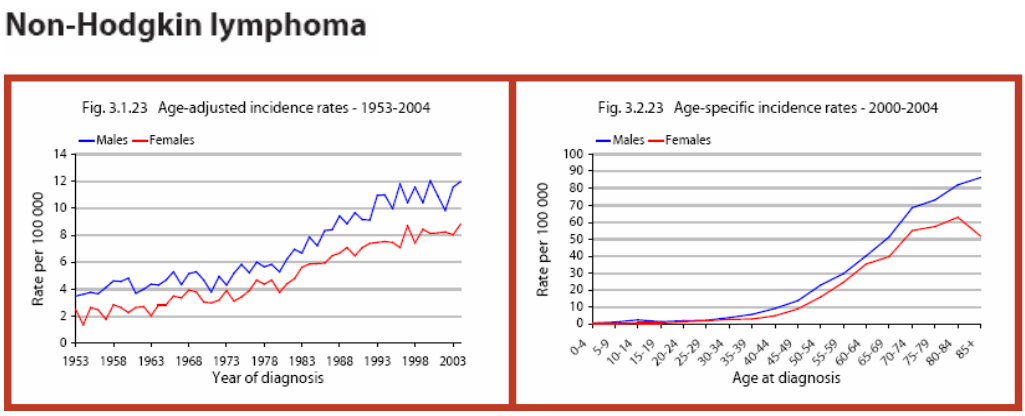


Fig. 2. Incidence of Non-Hodgkin´s Lymphoma [1]

Several histological classification systems have been proposed for NHL. The Kiel classification divides the NHL into the cell type of origin, principally T-cell or B-cell origin, and into low-grade and high-grade lymphomas, and has been used in Norway since the 1980s. In 1994 the REAL (Revised European-American Lymphoma) - classification was published, a revised classification system which quickly gained worldwide approval. In 2001 this was replaced by the WHO classification of lymphomas, which include both NHL and HD.[14, 15] In the WHO classification, the subdivision of low grade and high grade lymphoma is abandoned. Diffuse large B cell lymphoma, peripheral T cell lymphoma and follicular lymphoma (low grade lymphoma) is the main subgroups in the WHO classification group. Patients with NHL included in this thesis are classified by the Kiel-classification system (Table 2). For the staging of NHL the Ann Arbor staging system is used (Table 1).

Table 2. Kiel classification of Non-Hodgkin´s Lymphoma

B-Cell Neoplasms	T-Cell Neoplasms
Low-Grade Malignant Lymphoma • Lymphocytic • Lymphomaplasmacytic/cytoid • Plasmacytic • Centroblastic-centrocytic • Centrocytic (mantle cell) • Monocytoid	**Low-Grade malignant Lymphoma** • Lymphocytic • Small-cell cerebriform (mycosis fungoides, Sezary syndrome) • Lymphoepithelioid • Angioimmunoblastic • T-zone lymphoma • Pleomorphic, small cell
High-Grade Malignant Lymphoma • Centroblastic • Immunoblastic • Burkitts Lymphoma • Large-cell anaplastic • Lymphobastic	**High-Grade Malignant Lymphoma** • Pleomorphic, medium sized and large cell • T-immunoblastic • Large-cell anaplstic • T Lymphoblastic

Treatment and prognosis

It has been a dramatic development within the treatment of NHL during the last 10 to 15 years. Chemotherapy is the most important treatment modality for NHL, and extended use of combination chemotherapy regimen and the introduction of immunotherapy have improved the treatment results. Despite improvements in treatment, the mortality rates increases. While there is no gender differences in mortality rates of HD, women with NHL have somewhat better 5 years survival as compared to men (60% vs 55%). Stage, histological subtype and age are other important prognostic factors. The several treatment regimens for the different NHL are presented in the national treatment protocol (*Nasjonal Handlingsplan for maligne lymfomer, 2003, revised in 2004 and 2006).*

Chemotherapy

The majority of the patients with NHL (80-90%) have extensive disease. For patients with intermediate or high-grade NHL the CHOP-regimen have been considered as standard therapy. For patients with localized disease (stage I and II) most patients can be cured with chemotherapy only, as can 30-40% of patients with stage III and IV.[16] In order to improve the outcome, increasingly complex regimens were developed during the 1980s such as methotrexate, leucoverin, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (MACOP-B) - combination. Today, research within the molecular biology and target therapy has developed new treatment modalities also for lymphoma treatment. Immunotherapy with rituximab, a monoclonal antibody to the CD 20 antigene is today included in the standard treatment regimen in combination with CHOP for most of the NHL (CD20 positive).

Radiation therapy

The use of radiotherapy in the treatment of NHL depends upon histology, disease stage, and physiologic status of the patient. With more effective chemotherapy regimens, the technique of radiotherapy has been modified or even eliminated under some circumstances. It is included as standard treatment in combination with chemotherapy for patients with NHL stage I/II, or a single treatment modality for indolent NHL stage I/II, limited disease. The fields are to a great

extent similar to the fields used for HD. Fractional dosage of 2 Gy and a total dosage of 40 Gy are the most frequently applied doses.

High dose therapy and stem cell transplantation

Relapses in lymphoma patients younger than 65 years will be considered for high dose chemotherapy (HDC) and stem cell transplantation (SCT). The stem cells can be harvested from the patients pre-transplant, an autologous transplantation, or from an HLA (human leucocyte antigen)-matched donor, an allogenic transplantation. Bone marrow derived stem cells are considered as the classical stem cell source. Today, the peripheral blood progenitors (PBSC) is used as an alternative source for haematopoietic reconstitution, especially in autologous transplantation. Prior to the infusion of stem cells, the patients receive high doses of chemotherapy, in some patients in combination with total body irradiation (TBI) as part of the preparative regimen. In Norway, patients are treated with MIME (mitoguazon, ifosphamide, methotrexate, etoposid) as induction chemotherapy regimen, but cyclophosphamide containing chemotherapy regimen have also been applied. TBI has for many years been included in the preparative regime for patients undergoing transplant for lymphomas, especially for transplantation in patients with low-grade and lymphoblast lymphoma. However, many patients have received thoracic irradiation prior as part of the primary treatment, and due to many trials indicating a high risk of pulmonary toxicity related to radiotherapy, the use of TBI in HD is reduced.[17]

Late effects in patients treated for HD and NHL

Organ toxicities of the treatment modalities of HD and NHL are relatively well documented,[18-20] and studies of late effects from HD in children and other childhood cancers such as leukaemia and brain tumors have provided the foundation for research on late effects and long-term cancer survivorship.[2] However, the long-term and late effects of cancer and its treatment remain poorly documented and understood among those diagnosed as adults. Research on late effects in patients cured for cancer is challenging in many aspects and implies more than the study of organ toxicity alone. Although cancer survivors are living longer, limited knowledge exists about health status, functioning and quality of life for most of the patients treated for cancer.[2] The complexities of the

late effects themselves, the impact of late effects on their physical and psychosocial health and on HRQoL, and the effect of aging, lifestyle, behaviour and comorbidity on health status challenges the researchers in finding causal factors related to the outcomes observed. In particular there is a paucity of longitudinal cohort studies to link specific treatment regimens to late physical and psychosocial effects. Who are at risk for certain late effects, and who can be prevented are some of many questions related to cancer survivorship. Thus, it is not possible to describe the natural history of these events for future patients and for the health care providers.

Regarding lymphoma survivors most of the information on late medical effects stem from studies of HD treated by radiotherapy.[20] The majority of NHL patients are treated by chemotherapy. Studying late medical effects in NHL patients is more complicated. The age at peak incidence of NHL is above 40 years, for some subtypes even above 60 years. As the morbidity for most diseases increases by age, separating specific late effects from general morbidity poses methodological challenges related to design of studies and use of controls. Table 3 illustrates some described late medical effects among survivors of HD.

Table 3. Late medical effects observed in patients cured for Hodgkin's Disease

Late effect	**Causes and risk factors**
Immunologic dysfunction	Underlying disease, therapy
Herpes zoster or varicella	Underlying disease, therapy
Pneumococcal sepsis	Splenectomy, functional asplenia after RT
Nonlymphocytic leukemia	Therapy, older than 40 y
Myelodysplastic syndroms	Therapy, older than 40 y
Non Hodgkin's lymphoma	Therapy

Solid tumours	Direct or indirect RT exposure
Thymic hyperplasia	Underlying disease, therapy
Hypothyroidism	Direct or indirect RT exposure
Thyroid cancer	Direct or indirect RT exposure, chronic thyroid stimulation
Male infertility	Therapy, underlying disease
Male impotence	Therapy, underlying disease
Female infertility	Therapy
Female dyspareunia	Therapy, underlying disease
Pericarditis, acute	Mediastinal RT, recall with CT after RT
Pericarditis, chronic	Mediastinal RT
Cardiomyopathy	Mediastinal RT, doxoxrubicin, recall with CT after RT
Pneumonitis, acute	Direct or indirect RT, bleomycin, nitrosoureas, recall with CT after RT
Pneumonitis, chronic	Same as above
Avascular necrosis	Steroid therapy, underlying disease (?)
Growth retardation	Pediatric RT
Dental caries	Salivary change after RT

RT: Radiation therapy; CT: chemotherapy [21]

Second malignancies

Second malignancies are considered the most serious late effect observed in survivors of HD, and are currently the primary cause of mortality of these patients.[22] These late effects are probably the best documented late medical effects due to the valid comparison data obtained from the cancer registries. A long follow up period is required to obtain incidence data, and another challenge is that many patients have been treated with obsolete therapeutic regimens (i.e. mantle or extended field, MOPP chemotherapy).

Second malignancies after HD can be divided into three main categories: leukaemia, NHL and solid tumours. The risk of solid tumors exceeds that of leukaemia, and lung and breast cancer are the most common cancer diagnosis.[23, 24] Radiotherapy is the most important risk factor for both types of cancer. Other risk factors are age at first treatment, treatment modality, and radiation field and dose.[23, 25] Sarcoma, malignant melanoma, and thyroid cancer are other cancers which are found more frequent in patients treated for HD as compared to the general population.[24, 26]

Survivors of NHL are at increased risk for second malignancy, however much less than among HDS. This may be related to older age at diagnosis and less use of radiotherapy. An excess risk of leukemia and bladder cancer has been demonstrated to be treatment related, especially high dose cyclophosphamid regimen.

A strongly increased risk of leukaemia and myelodysplastic syndrome (MDS) following autologous bone marrow transplantation or peripheral stem cell transplantation for both NHL and HD is reported.[27]

Cardiovascular late effects

Cardiovascular diseases are considered the commonest non-malignant sources of excess morbidity and mortality among HDS and survivors of NHL, and provide difficult diagnostic and therapeutic dilemmas in the long-term care of patients after therapy.[28] The occurrence of radiation-induced heart diseases among patients treated for HD was recognized during the early era of high-dose mantle field irradiation. The clinical manifestations in the cardiovascular system range from asymptomatic pericardial effusion to fatal pancarditis, cardiomyopathy, myocardial infarction and vascular stenosis and thrombosis.[20]

A three fold increase in relative risk of cardiac death in patients treated for HD is reported, and the majority of the cardiac deaths are related to myocardial infarction probably due to development of premature coronary artery atherosclerosis.[29] The Stanford study also demonstrated a clear association with mediastinal irradiation and radiation dose, in that mediastinal irradiation to a dose of 30 Gy or less conferred no excess risk of cardiac complication and deaths. Young age at treatment and increasing time after completion of treatment is also associated with increased risk of myocardial infarction and death.

It is unclear whether or not the use of chemotherapy, in particular the increasing use of anthracyclines, will have a long-term effect on cardiac diseases. Anthracyclines are important antineoplastic drugs frequently used in combination with doxorubicin as one of the key component in the treatment of HD and NHL.[30] Cardiomyopathia and congestive heart failure are dose-limiting factors, which usually occur after doses greater than 550 mg/m2. A few studies have explored late cardiotoxicity after treatment with doxorubicin in adult HD and NHL patients.[31, 32] Most studies have been performed in children or in patients treated for acute leukaemia or breast cancer. In a study of long term adult survivors of lymphomas treated by doxorubicin, subclinical cardiac abnormalities were observed in the absence of congestive heart failure, and even after moderate doses of antracyclines.[33] Lund et al described abnormal left sided valvular regurgitation in one fourth of HDS investigated after mediastinal radiotherapy, and females were at increased risk.[34] The gender differences could not be explained by treatment-related differences or differences in baseline characteristics.

The risks of complications that lead to chronic heart diseases and premature mortality have been appreciated for more than one decade, and many centers and clinical trial groups have instituted changes in treatment programs in order to minimize these risks.[22, 31] The introduction of subcarinal blocking into the mantle field in 1972 in order to limit the radiation dose to myocard is one example. However, still important questions remain regarding long term effects. Few data exists on long-term excess risks of chemotherapy alone, while many series include several hundred patients treated with radiotherapy with median follow ups in excess of 10 years.[24, 35] Issues related to radiation dose effect are another important issue, and of particular interest since radiation remains the most effective single treatment modality for the treatment of HD. Finally, how should the patients be followed up after completition of therapy? Is it possible for the single oncologists to continue to follow the patients after treatment taking into consideration the

structure of the health care management, and the increasing number of cancer patients and cancer survivors? When do the patients have suspicious symptoms that demand a doctoral consult? Screening studies in detecting cardiac abnormalities in patients treated for HD is one possibility, however the value of such screening is unclear.

Pulmonary late effects

Pulmonary toxicity after radiation therapy for HD vary widely in presentation and severity and relate to volume of lung radiated, total radiation dose, dose rate, shielding techniques, radiation quality and undefined host factors that affect the extent of normal tissue reaction to irradiation.[29] The adverse effects range from acute interstitial pneumonitis to chronic lung injury such as pulmonary fibrosis and recurrent pleural effusions.[36, 37] Acute radiation pneumonitis can occur after radiation doses of more than 40 Gy to focal lung volumes or after lower doses (15-20 Gy) administered to whole lung and when combined with chemotherapy.[38] Chronic lung injury including pulmonary fibrosis and late recurring pleural effusions are reported to be related to high-dose, large-fraction therapy. The use of bleomycin- and anthracyclines-containing chemotherapy regimens such as ABVD are reported to enhance both short-term and chronic pulmonary toxicity from radiation therapy.[39]

The evaluation of the pulmonary status long after treatment for HD has however revealed different results.[29] Hassink et al reported significant pulmonary function abnormalities in HDS 14 years after radiotherapy with pulmonary symptoms such as dyspnoe reported by some patients.[40] Lund et al reported that nearly 30% of the 116 patients evaluated more than 5 years after HD therapy had symptomatic excertional dyspnoe and diminished lung capacity, forced vital capacity, forced expiratory volume and carbon monoxide diffusing capacity on pulmonary function tests.[41] The findings were associated with the combination of thoracic radiotherapy and bleomycin- or anthracycline based chemotherapy regimen, and are consistent with others studies of patients treated with these combined modality treatment.[39, 42, 43] Mantle field radiotherapy alone is found to be the most important factor associated with chronic reduction of forced vital capacity and diffusion capacity. In the absence of radiotherapy, bleomycin-induced pulmonary changes are usually mild and reverse over time, although Canellos et al reported clinically significant severe pulmonary toxicity in 6% of 115 patients treated with ABVD chemotherapy.[14, 39]

Endocrine late effects

Different endocrine abnormalities are observed after treatment for HD. Thyroid abnormalities attributed to HD treatment include hypothyroidism, hyperthyroidism and thyroid malignancies. These abnormalities are perhaps the most frequent clinical problems requiring evaluation and intervention after HD treatment with irradiation to cervical region and upper mediastinum. A 20-year actuarial risk of thyroid abnormalities of 50% is reported.[42, 44] Hypothyroidism is the commonest of these abnormalities with an incidence between 31%-90%.[42, 44] The majority of the patients are reported to have subclinical hypothyroidism with an abnormal elevation of thyroid-stimulating hormone and normal FT4 level. This has been a common finding in case of biochemical screening of HDS that have been irradiated, and the findings have been variably associated with clinical signs and symptoms of hypothyroidism.[29] Post irradiation hypothyroidism most often develop within the first 5 years after treatment, but some patients may develop hypothyroidism after 20 years or later. This challenges the physicians responsible for the follow up, how to diagnosticate correctly, when to start substitution therapy, and how to evaluate the effects of treatment.

Gonadal dysfunction is a well-known complication in the management of HD. Earlier, with extended field radiotherapy as a major treatment modality, gonadal dysfunction in women was a sufficiently significant problem to make oophoropexy a popular procedure in order to avoid infertility.[45] Pelvic radiation is an uncommon treatment modality today. The incidence of chemotherapy induced menopause in women varies by age. Patients above 40 years at the time of chemotherapy will frequently display induced menopause with related symptoms. Most patients under the age of 30 at the time of chemotherapy will remain fertile and over time regain normal menstruation.[46] The use of MOPP like regimen are most associated with irregular menstrual function and increase in follicular-stimulating hormone (FSH) and luteinizing hormone (LH), whereas the ABVD seems to spare menstrual function and fertility in women.

Infertility in males is a major complication after chemotherapy for HD. The possibility to recover normal spermatogenesis depends upon the type of chemotherapy regimen. After MOPP-like regimens recovery of spermatogenesis after a full course of chemotherapy is unusual, the chances are reported to be 5-14%. The FSH and LH will often be increased after therapy, although testosterone levels remain normal. In contrast, nearly all patients receiving the present standard chemotherapy regimen (ABVD) will eventually recover normal spermatogenesis.[47]

Immunological late effects

In cancer patients, the immune system may be altered by the underlying malignant disease or by the treatment. Long term immunosuppressive effects in patients treated for HD have been demonstrated after both radiation therapy, chemotherapy and combined modality treatment.[48-50] These long term effects include decrease in the number or function of the T lymphocytes, especially the helper T-cell subset, as well as decreased response to peripheral blood lymphocytes to mitogens. Abnormalities of the cellular immune system in even untreated patients with HD is also documented.[48, 50] This may explain the increased susceptibility for certain infections such as Herpes Zoster and tuberculosis, that may even appear in untreated HD patients. However, both chemotherapy and radiotherapy, splenectomy or splenic radiotherapy, may accentuate immunosuppresive effects and increase the risk of serious bacterial and viral infections. Herpes Zoster is the most common infectious disease in patients treated for HD, and the risk is highest within the first two years after ended therapy, however for some patients remains a life long risk. A long-term infectious risk also exists for gram positive S. pneumoniae and meningococcus which may cause fatal sepsis. For splenectomised patients a potential high long term risk for this infection will remain in the follow up.[51]

Neurological and neuropsychological late effects

Several of the chemotherapeutic agents used in the treatment of HD and NHL can cause neurotoxicity alone, or in combination with radiation therapy. The most common chemotherapy agents used in the treatment of HD/NHL that have been associated with neurotoxicity are the vinca alkyloids such as vincristine and vinblastin. Neurotoxicity is caused by destruction of neurotubulus, most often presented as peripheral neuropathy with sensibility loss and impaired muscle strength.[52] Cytarabine and methotrexate administered intravenously or intrathecally can cause meningeal irritation, paresis, encephalopathy or memory loss. Radiotherapy of the CNS increase the risk of neurotoxicty and is associated with encephalopathy and deficits in cognitive function.[53]

As demonstrated in recent reviews of the literature, cognitive deficits have been recognized as a problem among adult cancer survivors.[53, 54 55] The most frequently reported cognitive domains being vulnerable to chemotherapy are attention, memory and executive functions, which all may

affect the activities of daily living, educational and working abilities. Cognitive deficits may therefore have dramatic effects on patients HRQoL, and ability to function even when the cognitive impairments are mild. Subtle changes are however difficult to identify because of lack of appropriate measures.[56] Studies of breast cancer patients treated with high dose chemotherapy and autologous stem cell support reported more cognitive impairments and impaired HRQoL 2 years after therapy as compared to those treated with standard chemotherapy.[57] Additionally, more late cognitive impairments were observed in the latter group as compared to those not treated with chemotherapy. Cull et al reported in her study of adult disease free lymphoma patients or > 6months after therapy that those who reported cognitive problems such as memory and concentrating difficulties also reported more anxiety, depression and fatigue indicating an additional methodology challenge in evaluating impairments in higher mental function in cancer survivors.[58]

Late effects after high dose therapy and stem cell transplantation

Patients treated with high dose therapy and stem cell transplantation are at increased risk for late effects both associated to the primary disease, the primary treatment and the high dose therapy per se. In general, the incidence of complications after high dose therapy is similar to those reported after standard therapy. A major concern is the possibility to develop myelodysplasia or acute myeloid leukaemia, and in particular after TBI.[27] Hypothyroidism, sexual dysfunction and late infections such as Herpes zoster, pneumonia and infections in the urinary tract are frequent complications in lymphoma patients after BMT or ASCT.[59]

Quality of life and health related quality of life

Assessment

HRQoL are subjective and consequently not directly observable or measurable. HRQoL are most commonly measured by questionnaires that are filled in by the patients. The instruments may be generic, in order to asses HRQoL in general populations; disease specific e.g. developed for cancer patients or domain specific assessing symptoms such as fatigue.[60] The instrument needs to fulfil a set of requirements to produce valid and reliable results in clinical research. Most important are the basic properties, i.e. validity, reliability, sensitivity and responsiveness.[61] Reliability refers to the accuracy and consistency of the measure. The more reliable a measure is, the lower is the element of random error. Validity is the degree to which the measure reflects what it is intended to measure. Sensitivity and responsiveness are closely related, and whereas sensitivity refers to the ability to detect differences between patients or groups of patients, responsiveness is the ability of a measure to detect underlying change within the patients.[61]

Several HRQoL instruments are developed and the most commonly used in cancer patients is the EORTC QLQ-C30.[62] It is composed of five functional scales (physical, emotional, cognitive, social, role), three symptom scales (fatigue, pain, nausea) and five single items measuring dyspnoe, vomiting, appetite loss, constipation and financial impact of disease. Additionally global health and overall quality of life is measured (see appendix for the entire questionnaire).

Fatigue

Concept and terminology

Fatigue is commonly defined as a non-specific and subjective feeling of tiredness, physically and/or mentally.[63] The multidimensionality of fatigue is partly grounded on theoretical and empirical data from cancer patients,[64-66] patients with non-malignant diseases,[67, 68] as well as disease-free cancer survivors.[4, 69, 70] There are a number of current debates related to the number and types of dimensions. It is most commonly to divide fatigue into two dimensions, mental and physical fatigue, however, others have also been proposed.[64]

Fatigue can be acute or chronic. Acute fatigue includes for example the subjective feeling of being ill during a common flu, the feeling of diminished energy during radiotherapy or the feeling of exhaustion after physical exercise. Fatigue lasting for 6 months or longer is by most researchers defined as chronic.[71] In order to understand the concept and to plan treatment, an extensive understanding of the underlying pathophysiology (i.e. causal factors). These mechanisms are often more easily detected in acute than in chronic fatigue. Chronic fatigue may vary over time in intensity, being context dependent and occur in varying frequency and intensity in well defined cohorts. Chronic fatigue will in most patients also include the effects of behavioural adaption over time.

Assessment of fatigue

Fatigue was regarded as a central medical symptom during the second half of the 19th century.[63] [72] Several approaches to measurement of fatigue have been used throughout the history such as observation, self-rating and objective tests.[65, 73-75] Self rating measures are the gold standard and most commonly used today. The measures can be divided into single –item and multi-item instruments. The latter might be uni- or multidimensional. As mentioned previously, fatigue is often included as a domain within the HRQoL concept. Subscales measuring fatigue are therefore included in the generic HRQoL instruments, such as the SF-36 (i.e. not specific to any population or disease), as well as disease-specific instruments, such as the EORTC QLQ-C30.[76] [62]

Several domain specific instruments specifically designed for measuring fatigue are also available.[66, 77-81] Although most researchers state that fatigue is a multidimensional phenomenon, the number and content of dimensions (as already discussed in this thesis) are debated, and the various instruments reflect this. However, all present fatigue-measures include physical fatigue, which corresponds to the subjective feeling of being exhausted and lacking energy. In advanced metastatic disease, fatigue is commonly viewed as uni-dimensional, ie a reflection of general illness.[82] Due to clinical experience and descriptive studies, palliative cancer patients report not only impaired physical performance, but they are also mentally alert with concentration difficulties and impaired memory, symptoms of mental fatigue. Unidimensional fatigue measures will probably exclude the possibility of a complete description of the fatigue experience of cancer patients.

The prevalence of fatigue

Fatigue in the general population

Fatigue is a common complaint within the general population, with approximately 10% reporting a clinical significant level of fatigue.[74, 83, 84] Fatigue is also highly prevalent among attenders in the primary health care (20-30%).[85]

Fatigue in somatic and mental diseases

Fatigue is a major symptom in a whole range of somatic conditions, including acute viral and bacterial infections as well as neurological diseases, such as multiple sclerosis (MS), post poliomyelitis and post stroke. It is a cardinal symptom of chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, in kidney disease, in chronic heart failure and chronic obstructive pulmonary diseases.[65, 68, 86-90]

Fatigue is one of the nine criteria for major depression according to the DSM-IV.[91] Fatigue correlates strongly with psychological distress in the general population.[84] Depression and anxiety are also the most stable associations of chronic fatigue in primary care.[63] In somatically ill patients, however, it is difficult to differ between depressive and fatigue symptoms. Fatigue may be a result of depressed mood, and a person who continuously perceives his or her energy as insufficient may become depressed. [92]

Fatigue in cancer patients

Fatigue has been described as a nearly universal symptom among cancer patients.[93] It might be a first symptom of cancer, a side effect of cancer treatment or a prominent symptom of terminal disease. Fatigue is highly prevalent among cancer patients undergoing cytotoxic chemotherapy, radiation therapy, bone marrow transplant or treatment with biological response modifiers.[65, 94-101] However, there is a lack of systematic studies addressing the prevalence across diagnoses and phases of the disease, the intergroup (diagnosis) variability in cancer as well as variations according to stage of disease and phase of the illness. A limited number of studies of fatigue in relation to type of

treatment are available.[65, 97, 100-104] The sample sizes in these studies are small, and fatigue has been measured with different instrument and at different point in time according to treatment and diagnosis, and suitable comparison groups are seldom included. This makes comparison difficult between studies. Most of the studies are cross-sectional, and valid estimation of the duration is therefore seldom available.[105, 106]

One of the first studies addressing fatigue in cancer survivors were published in 1986.[107] In this follow up study of HDS, 37% reported that the energy level was not returned to normal after end of therapy. Relatively few studies have later investigated fatigue in cancer survivors. Studies of adult long term survivors of childhood cancer have not demonstrated long-lasting fatigue after cancer cure.[105, 108] Various data exist on fatigue in survivors of breast cancer. Lindley et at failed to demonstrate increased fatigue post treatment for early stage breast cancer.[106] A recent longitudinal study of fatigue in long term breast carcinoma survivors indicated that 34% of the women were fatigued 5-10 years after diagnosis.[109] Among long-term survivors of testicular cancer, 16% reported chronic fatigue.[110] Fatigue is still reported to be a frequent symptom among HDS, and affects up to 1/4 of the HDS.[4, 107, 111] The symptom seems to persist several years after treatment.[112] Except for higher level of fatigue in patients with stage IB/IIB of the disease, no relationship between fatigue and disease characteristics or type of treatment have been found.[4] A recent study support these finding in that no association between fatigue and type of treatment over time were found.[113] Different instruments used to measure fatigue, choice of comparison groups and cross sectional designs limit the possibility to draw firm conclusions.

Possible etiology of fatigue

General comments

Many possible causes and factors related to the etiology of fatigue have been suggested in the literature, but relative few hypotheses have however been testable regarding the etiology of this symptom. Take into consideration the prevalence of the symptoms across quite different patient groups, it is likely that several mechanisms underlie fatigue, and that they probably vary between populations as well as within populations.

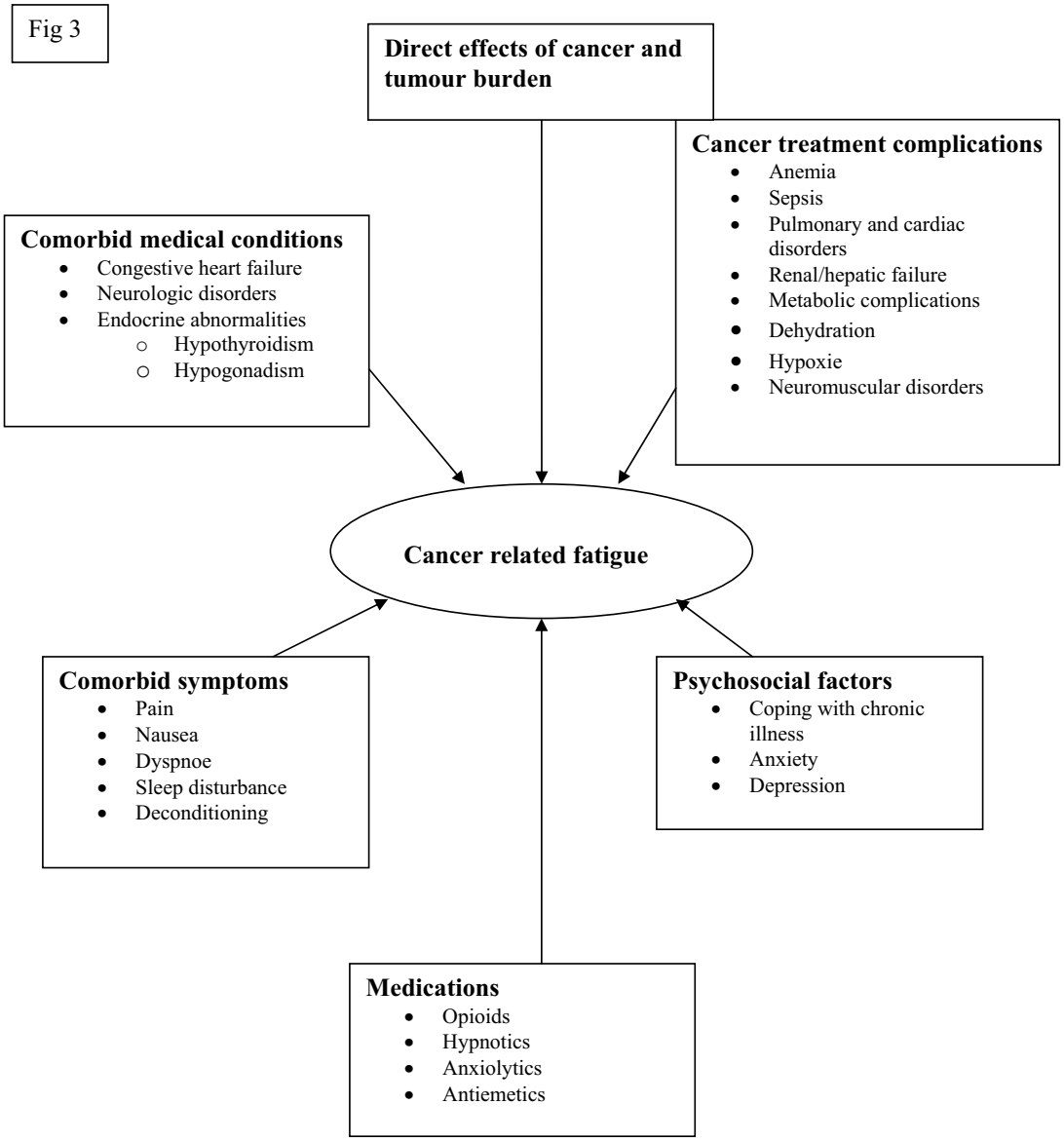
Almost all studies of fatigue are cross-sectional, which makes it difficult to draw causal relationships. What might look like highly significant predictors in cross-sectional studies might be

confounding effects. Confounding implies that underlying factor(s) explain both the predictor and the outcome (i.e. fatigue). The cancer disease itself might be the confounder in cancer patients with active disease. This is supported by a study of pain and fatigue in elderly cancer patients, which demonstrated that both fatigue and pain were explained by the same disease variables.[114]

Inactivity, sleep disturbances and psychological distress are commonly observed in most diseases, and have all been associated with fatigue. Other factors that have been associated with fatigue such as pain and anaemia are not necessarily observed in all diseases, or may be relevant contributing factors in cancer patients but not in disease free cancer patients. In cancer patients without active disease other factors may play important roles such as pathophysiologic mechanisms to disease- and treatment related late effect (i.e. alterations in immune and neuroendocrine function). Medical conditions, genetic factors and personality characteristics are not investigated extensively.

Few studies have documented a causal relationship between a pathological process (for example a particular late effect) and cancer-related fatigue. For some symptoms such as nausea and pain there are specific neuronal pathways, which convey the message from the affected part of the body to the brain where the information is processed and eventually expressed. In our clinical settings we can therefore assume that the subjective sensation (pain) reflects an underlying pathological process (for example bone metastasis) that has activated the neuronal pathway, and one will treat the bone metastasis, for example with radiotherapy, to relief the pain. However, no such neuronal pathway has been documented for cancer-related fatigue. Fig. 3 gives an overview over possible relevant factors for developing cancer-related fatigue.

Fig 3



(Modified figure [115])

The literature presents several figures and tables with lists of possible etiologic explanations to fatigue. The problems with these lists are multiple: Several of the factors and conditions are non specific factors and conditions which "always" will be accompanied with fatigue, such as sepsis, and dehydration. These factors are not specific for cancer related fatigue. The lists do not differ between acute and chronic fatigue, and acute fatigue will usually be relieved by successful treatment of the condition responsible (ie sepsis). The causes to chronic fatigue in cancer patients are seldom explored, and it is probably a more complex phenomenon hardly possible to explain by single factors. The hypothesis of the etiology of fatigue can alternatively be presented as models.

Models of fatigue in cancer

Some models of fatigue in cancer have been presented during the last decades. Piper et al developed one of the first integrated models of fatigue in cancer which explained the multidimensional and complex nature of fatigue, including biochemical, behavioural, social and psychological influence.[116] The model by Nail and Winningham stress the role of other symptom of cancer and their influence on developing fatigue.[117] They explain that symptoms such as pain, nausea or immobility might lead to inactivity, promoting the development of secondary fatigue. Further research have supported the hypothesis of secondary fatigue, describing a vicious circle, leading to activity/rest imbalance: unusual tiredness (fatigue) leads to increased need for rest, leading to activity intolerance, to weakness, to reduced physical performance, and finally again to increased fatigue.[118] These models again lack a critical evaluation of which pathophysiological factors that may play a role. The models do not recognize possible biological variables that may be relevant for fatigue.

Cytokines

The role of cytokines in cancer-related fatigue is incidentally discussed by several researchers.[102, 119-122] Both cancer and its treatment by chemotherapy, radiotherapy and surgery elevate the levels of the pro-inflammatory cytokine TNF and of IL-1 and IL-6, which are products in a cytokine cascade. Cytokines are protein-signalling molecules with specific receptors and complex biological effects. They can be produced by many cell types including fibroblast, neurons, astrocytes, macrophages, tumours and epithelial cells of various types.

The biochemical and clinical effects are complex and are mediated by a number of signalling pathways.[102]

The hypothesis that cytokines may play a role in cancer-related fatigue is consistent with various clinical studies and observations. One of the first article indicating that cytokines was associated with cancer-related fatigue was published in 1993.[123] The authors demonstrated an increase in interleukin-1B (IL-1) during radiotherapy parallel to an increase in fatigue. Several researchers have found elevated levels of cytokines in patients reporting chronic fatigue. Later empirical studies have failed to demonstrate significant associations between various cytokines and fatigue.[124, 125] Still, there is growing evidence that cytokines both experimentally and clinically are messengers that trigger manifestations of disease such as fever, cachexia and anemia as well as several symptoms including fatigue, all commonly associated with cancer.[122] Cytokines can alter brain functions, and the research on the effects of cytokines on disease manifestations is rapidly growing.[121, 126] Cytokines may also play a role in sleep regulation, which may be of particular relevance for fatigue.[127] There are also indications that cytokines are the mediators of sickness behaviour.[128] In sum, the results of various studies of cytokines indicate they may have psychobiological effects which may cause fatigue.

Anemia

Anemia is also frequently discussed as a cause to fatigue. Blunted endogenous erythropoietin response, cytokines induced erythropoiesis suppression (IL-1, IL-2, IL-6 and TNF that suppress red blood cell production), functional iron deficiency (even when their iron levels appear normal), and finally chemotherapy-induced bone marrow suppression, bone-marrow infiltration and bleeding are possible etiologic factors of mechanisms behind cancer related anemia.[122] Several studies have demonstrated that anemic cancer patients are more fatigued than non anemic cancer patients, and that treatment of anemia can result in less fatigue and improved quality of life.[129-133] The findings concerning the effects of haemoglobin level upon fatigue is however conflicting. Lind et al reported that only 8 % of the variation in fatigue scores in cancer patients could be explained by anemia.[132] In a study of fatigue in elderly cancer patients above 60 years, a statistically significant but weak correlation was found between fatigue severity and anemia ($r=-0.30$, $p<0.01$).[134] Furthermore, a prospective

controlled study of palliative patients failed to demonstrate any effect of haemoglobin level upon fatigue,[135] and the effects of correction of anemiae upon fatigue are also disputed.[136]

Anaemia is not as common in cancer patients treated with radiotherapy although such patients typically report more fatigue than chemotherapy patients. Furthermore, several studies have reported an increase in "energy" or QoL in patients with anaemia being treated with recombinant human erythropoietin alpha (rHuEPO), but the precise relationship between fatigue and measures of "energy" and QoL remains to be identified.[102, 130, 137] In most of the studies a variety of outcomes have been used, which hampers the interpretation of the findings.

Psychological disorders and sleep disturbances

Psychological factors have been suggested in some studies to be associated with cancer-related fatigue.[125, 138, 139] but the results have been contradictory, and a causal relationship has not been demonstrated.[140] A strong correlation between the intensity of fatigue and psychological disorders such as depression was found in cancer patients.[141] In contrast, Visser et al reported only a modest correlation between fatigue and depression in cancer patients undergoing radiotherapy.[92] The relationship between fatigue and depression is clearly complex in that fatigue is one of the nine criteria for depression according to the DSM-IV,[91] but not necessary indicated depression, and may also be a consequence of being depressed.

Sleep disturbance are common in cancer patients, but few studies have addressed this.[142] There are different types of sleep disorders, which are all accompanied by fatigue. These include insomnia, hypersomnia, narcolepsy, and obstructive sleep apnoea and circadian rhythm sleep disorders. Insomnia and hypersomnia have been found to be prevalent and evidence is accumulating on the prevalence of sleep disorders in cancer patients.[143] Although not fully explored, cancer treatments including opioids also alter the circadian rhythm. A recent study demonstrated that fatigue, mood and depression were significantly associated with concurrent changes in circadian rhythm.[144] Fatigue during radiotherapy was best explained by the pre-treatment level of fatigue, which was highly related to sleep disturbance [145] whereas in another study increased sleep requirement and radiation induced fatigue were associated to a systemic reaction of increased inflammatory cytokine interleukin-1.[123]

Possible etiology to fatigue in non-cancer patients

Fatigue is a cardinal symptom of MS and systemic lupus erythematosus, and the severity of the symptom will often reflect disease activity.[68, 146, 147] Studies have demonstrated a correlation between fatigue and increased circulation immune activation.[127, 148] Medications such as interferon-α and – β produce prominent fatigue as an adverse effect. [149] Analogous, fatigue is reported to be associated with the systemic effects of the immune activation in patients with chronic heart failure.[150, 151]

In patients with chronic lung diseases, the mechanism to fatigue is not completely clear. Fatigue is additionally to dyspnoea the two most common symptoms in patients with chronic obstructive pulmonary disease (COPD). Clinical experience and studies have demonstrated that the two symptoms are highly correlated in COPD patients, perhaps because the mechanism are unclear and likely overlap.[152] The decline in cognitive function indicating symptoms of mental fatigue observed in COPD patients are proposed to be related to a decrease in oxygen transport to the brain.[153] Arterial oxygen desaturation in these patients may develop as result of their disease.[154] Pulmonary abnormalities results in arterial oxygen desaturation with resultant dyspnoea during activity, which again result in avoidance of activity and further deconditioning.[153] Reports of positive relationship between exercise related improved oxygen use and improved fatigue/dyspnoea, and between aerobic exercise and cognitive function support this assumption.[152, 153]

Fatigue is also related to disturbances in the hypothalamic-pituitary-adrenal axis (HPA).[155, 156] In diseases or conditions related to an underactive HPA-axis, fatigue may be caused by the proinflammatory cytokines that become activated by reduces corticotropin releasing factor and low cortisone concentration.[153, 156] Disturbance in the HPA axis and low level of cortisone have been reported in some studies of sufferers of chronic fatigue syndrome.[157] Development of sudden and profound chronic fatigue in physically active and highly motivated sportspeople (overtrained athlete syndrome) is also affected by hypothalamic and related neuroendocrine changes.[158]

Possible etiology of fatigue in cancer survivors

In 1987 Devlen et al performed a prospective study of the psychological and social morbidity following the diagnoses and treatment of HD and NHL.[159, 160] Frequent complaints of tiredness (32%), loss of energy (43%), poor concentration (15%) and memory impairment (19%) were found. Although the authors found that these symptoms were associated with increasing age, anxiety and depression, they also suggested that these represented minor cerebral damage due to central effects of chemotherapy or viral infection during periods of immunosuppression.[160] In the same study, it was also emphasized the use of magnetic resonance imaging (MRI) as a sensitive method to gain objective evidence of cerebral damage.[161] In children with neurological and neuropsychological treatment related sequelae, MRI have demonstrated white matter changes and periventricular/subcortical changes even in patients with mild symptoms not uncovered by other neurological means of investigation.[161] These hypotheses have not been investigated in studies of fatigue in HDS later. In non cancer patients, however, studies have demonstrated an association between fatigue and similar MRI findings.[162-165]

Greenberg et al was one of the first to report an association between fatigue and cytokines due to the ability of proinflammatory cytokines to signal the central nervous system to induce symptoms of fatigue and other "sickness behaviour ".[123] The hypothesis that inflammatory alterations underlie chronic fatigue in cancer survivors is of special relevans in the study of fatigue in HDS due to the biological components of HD. The cytokine hypothesis and dysregulation in the HPA-axis is also the underlying theory in several of the recent and ongoing studies of chronic fatigue in breast cancer survivors.[166-168]

The few studies of long term cancer survivors conducted until now have also suggested that chronic fatigue may be related to late effects of treatment.[69, 107, 113] In 1996 a Norwegian study demonstrated that patients treated with mantle field irradiation had higher risk of dyspnoea leading to higher fatigue score and lower quality of life.[169] Lund et at could in her thesis demonstrate cardiopulmonary sequelae in more than half of otherwise healthy long term HDS which all had been treated with radiotherapy alone or in combination with chemotherapy.[170] Later studies of the same patient cohort demonstrated a 2-3 fold increased level of chronic fatigue as compared to norms from the general population.[4] Taking into consideration observations of fatigue in non cancer patients with cardiac and pulmonary diseases, it is reasonable to question whether chronic fatigue in HDS represents symptoms of late somatic

complications after cancer treatment. This research question has not been investigated in studies earlier. Consistent with this, specific research on the role of endocrine late effects such as hypothyreosis and gonadal dysfunction in the etiology of fatigue in HDS have not been performed.

A critical moment for an accurate understanding of chronic fatigue in cancer survivors is the knowledge about fatigue before treatment and ideally during the treatment period. In the only prospective report on fatigue in HDS, Ganz et al demonstrated that fatigue was a substantial problem in patients with HD before treatment and did not decrease after ending treatment.[113] As discussed in the paper, this may indicate that fatigue is related to inflammatory processes caused by the underlying disease or by effects of the treatment.[113] Hjermstad et al described prospectively the trajectory of fatigue and other HRQoL domains including anxiety and depression in lymphoma and leukaemia patients before, during and 1 year after HDC and ASCT/SCT.[171] The lymphoma patients reported more fatigue and other symptoms and worse function on most of the HRQoL domains before and 1 year after treatment as compared to the leukaemia patients. If this pattern persists in an extended follow study above 1 year after treatment, the observation will support the postulation that fatigue in lymphoma patients is related to the disease itself or to certain effects of the disease or the treatment given.

Aims of the study

The overall aim of this thesis is to increase the understanding of fatigue. The focus is on the frequency, the assessment methodology and the etiology of the phenomenon.

- Methodological issues in assessment of fatigue in patients with advanced disease as well as in cancer survivors are addressed in Paper I, and the research questions were as follows:

    - Does the EORTC QLQ-C30 fatigue scale measure mainly physical fatigue?
    - Does the EORTC QLQ-C30 fatigue scale demonstrate a poorer sensitivity in measuring fatigue as compared to the domain specific Fatigue Questionnaire?

- Prospective design with follow up extending at least one year post treatment is probably the best method of assessing fluctuations and symptom burden during and after cancer treatment. Paper II address subjective health in patients with hematooncologial malignancy during and until 3-5 years after high dose chemotherapy and stem cell transplantation with specific focus on fatigue. Based on clinical experience and previous work two main research questions were raised:

    - Do lymphoma patients 3-5 years after transplant report lower function, more symptomatology and poorer overall quality of life as compared to leukemia patients after transplant?
    - Do lymphoma patients report more fatigue 3-5 years after transplant as compared to leukaemia patients and compared to general population?

- Fatigue is a multidimensional and multifactorial phenomenon. The pathophysiological mechanisms involved are not well understood. In order to

improve the understanding of etiological factors the following research questions were raised, and these are adressed in paper III – V:

- What is the explanatory value of cardiac, pulmonary and endocrine complications on fatigue in HDS?
- Is fatigue in HDS related to abnormalities in central nervous system or alterations in the immune system, and what are the possible causes?

Material and Methods

Study population and design

Five different cohorts are included in this thesis. A series of different outcomes in addition to fatigue were used in the various cohorts. Table 4 gives an overview of the populations, primary and secondary outcome as well as the study designs. Furthermore the links between the cohorts and the various papers are briefly given.

Table 4. Study populations, design and outcome

Populations	**1**	**2**	**3**	**4**	**5**
Hospital	Multisenter study (Norwegian/Swedish hosp.)	NRH/NH	NRH	NRH	TUH
Diagnosis	Advanced cancer with bone metastases	Leukaemia/NHL/ HD	NHL/HD	HD	HD
Treatment	Palliative radiotherapy	HDC/SCT/ASCT or Standard treatment	HDC/ABMT	Standard treatment	Standard treatment
Treatment period	1998-2000	1993-1996	1987-1993	1980-1988	1987-1997
Number	N=238	N=180	N=33	N=92	N=27
Design	Prospective	Prospective	Cross sectional	Cross sectional	Cross sectional

Outcomes	Fatigue (FQ/EORTC QLQ-C30) HRQoL (EORTC QLQ-C30)	Fatigue (FQ/EORTC QLQ-C30) HRQoL (EORTC QLQ-C30) Anxiety/depression (HADS)	Fatigue (FQ/EORTC QLQ-C30) HRQoL (EORTC QLQ-C30) Endocrine function Cytokines	Fatigue (FQ)	Fatigue (FQ) Brain MRI
Paper	I	I / II	III	IV	V

NRH: Norwegian Radium Hospital; NH: National Hospital Norway; TUH: Trondheim University Hospital; FQ: Fatigue Questionnaire; HADS: Hospital Anxiety and Depression Scale; HD: Hodgkin´s Disease; NHL: Non-Hodgkin´s Lymphoma; HDC: High dose chemotherapy; SCT: Allogenic stem cell transplantation; ASCT: Autologous stem cell transplantation; ABMT: Autologous bone marrow transplantation;

Study populations

1. **Palliative cancer patients with bone metastases**

Patients with advanced cancer and painful bone metastases were recruited in the period from 1998-2000, to participate in a randomised clinical trial comparing the effect of standard radiotherapy versus hypofractioned radiotherapy. The cancer diagnoses were mixed, with the majority suffering from breast and prostate cancer. The patients should have bone metastasis verified by mean of x-ray, bone scan, computer tomography (CT) or MRI. There were no limitations with the site of the bone metastases. The patients should have a Karnofsky Performance status equal to or above 40, and the bone metastases should result in clinically important pain judged by the physician and the patient. The first 249 randomized patients were included in the present study (Paper I). Patients completed the EORTC QLQ-C30 and the Fatigue Questionnaire (FQ) at study entry and thereafter every month for 6 months (28 weeks) or until death. The assessments at study entry (T0) and after 12 weeks (T12) and 28 weeks (T28) were used in the present analysis. In Paper I, an additional cohort was included; Patients with leukaemia and malignant lymphoma curatively treated with stem cell transplantation and high dose chemotherapy (cohort 2, n=128).

2. Leukaemia/Non-Hodgkin/Hodgkin´s Disease, high dose chemotherapy 1993-1996

In a three years period from 1993 to 1996 all consecutive leukaemia patients admitted for high dose chemotherapy (HDC) followed by allogeneic bone marrow or blood stem cell transplantation (SCT) at the National Hospital (NH) were invited to participate. All consecutive patients with HD or NHL treated with HDC and reinfusion of autologous bone marrow or blood stem cells (ASCT) at the Norwegian Radium Hospital (NRH) were also included. At the same time, all patients who were admitted to the NRH for diagnostic verification of HD or NHL, and start of standard treatment, were invited to participate in the study as a comparison group. The recruitment of patients and participating rates is described elsewhere.[172]

Of the 76 SCT patients, 85 ASCT patients and 161 CT patients who were initially approached, the baseline questionnaires at the time of study entry were completed by 62, 69

and 123 patients respectively. One SCT patient and five CT patients were excluded from the analyses because only the first questionnaire was filled in due to critical illness and death. Over the years of follow-up, 16 SCT patients, 14 ASCT patients and 20 CT patients died, while 10, 15 and 27 patients respectively withdrew. Due to practical reasons, the last evaluation at least 3 years post transplant was performed as a cross-sectional assessment. The EORTC QLQ-C30, the Hospital Anxiety and Depression Scale (HADS) and the FQ were mailed to the 141 eligible patients (SCT, n = 38) or autologous stem cell transplantation (ASCT, n = 42) (CT, n=61). The response-rates at the last assessment were 92%, 95% and 87% respectively (Figure 4a-c).

Figure 4a.

Attrition of patients from approach to minimum 3 years of follow up.

SCT group

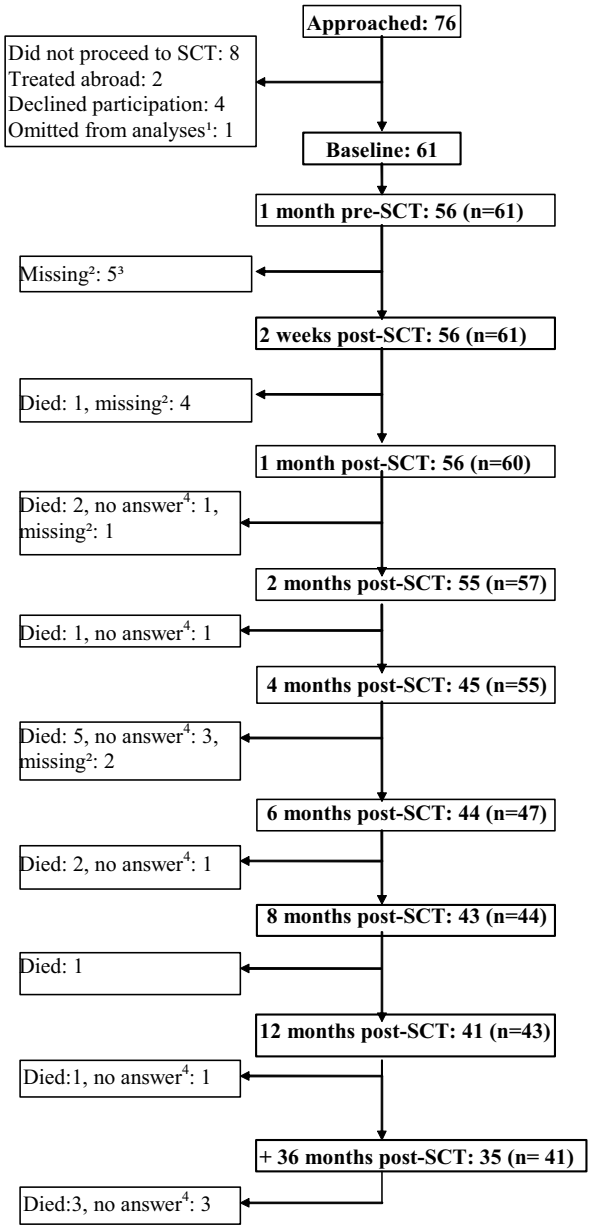


Figure 4b. ASCT group.

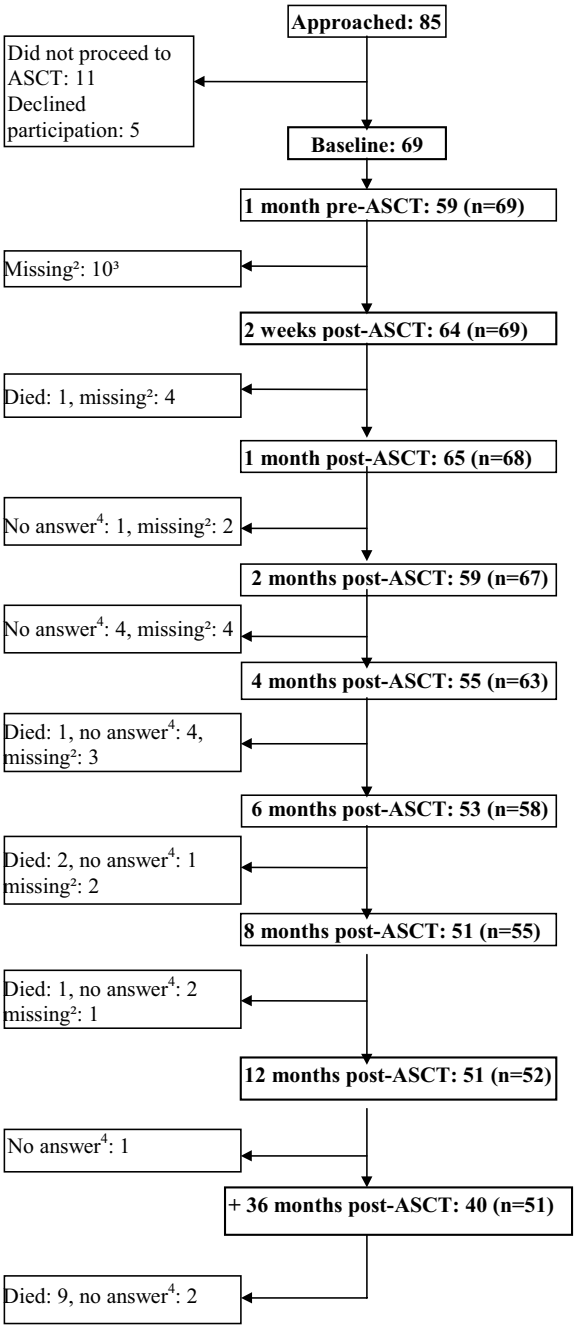
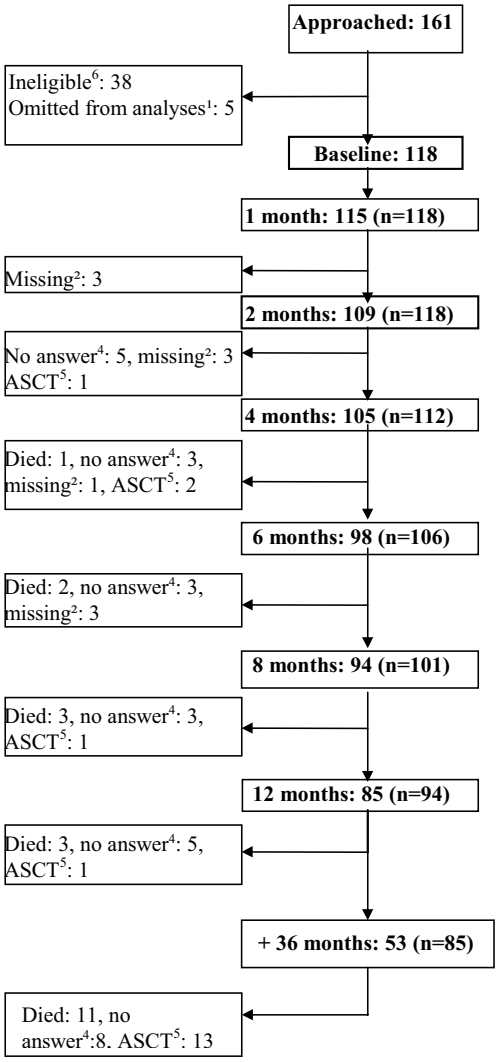


Figure 4c. CT group.



[1] patients who filled in the first questionnaire only

[2] patients who failed to fill in a single questionnaire, but who wanted to remain in the study

[3] because inclusion was less than one month prior to transplant, questionnaires were not administered to five SCT and nine ASCT patients

[4] patients who failed to respond after one reminder or who declined further participation on the provided statement coupons: withdrawn from the sample

[5] accepted onto the ASCT programme due to relapse or disease progression

[6] due to: benign disease (1), no treatment (3), radiotherapy only (20), low intensive treatment with Chlorambucil and Prednison (14)

3. Non-Hodgkin/Hodgkin´s Disease, high dose chemotherapy 1987-1993

From 1987 until ultimo 1993 all 85 cases of malignant lymphomas requiring autologous bone marrow transplantation (ABMT) in Norway were treated at the NRH. In January 1997 46 patients were alive, in complete remission (CR) and invited by mail to participate in this study. In order to assess late side effects after ABMT, patients with a follow up of three years or more were approached. One refused to see a new doctor, another answered too late for inclusion, one had moved abroad, and four patients did not answer to the request. This led to 39 patients, and 38 patients of these completed the mailed questionnaires, the EORTC QLQ-C30 and FQ. Before the clinical work up, three patients declined to participate due to hospitalization because of cerebral insult, myelodysplastic syndrome or major psychiatric problems. Two of the blood samples were damaged during transportation, thus 33 serum samples were valid for use. These 33 patients comprised the material in Paper III.

4. Hodgkin´s Disease Survivors, Norwegian Radium Hospital, 1980-1988

All living patients treated for HD at the NRH in the period between 1971 and 1991, 15 to 61 years of age at the time of diagnosis, and 74 years or less by the end of 1993 were invited to participate in a cross- sectional follow-up study of subjective health. In 1994, 559 HDS received a mailed questionnaire, and 459 patients (82%) responded.[4] A subcohort of these subjects, limited to patients who had been treated between 1980 and 1988 with standardized mediastinal radiotherapy alone or in combination with chemotherapy, were included in a second study in order to assess long term cardiac and pulmonary complications. Thyroid status was also assessed. Patients aged 50 years or younger at the time of diagnosis and who had been in complete remission for more than 5 years at the time of follow-up were invited to participate. In the study, 116 of 129 eligible patients were included (90%).[41, 170, 173]

In Paper IV we included all the patients who participated in both of the above mentioned studies (n=92).

5. Hodgkin´s Disease Survivors, Trondheim University Hospital, 1987-1997

Starting in 1987, all patients with HD living in middle part of Norway were treated at the Trondheim University Hospital. Sixty-two patients was treated in the period from 1987-1997, alive without evidence of active disease in 1999 and aged from 19 to 74 years. These were eligible for a follow-up study. A questionnaire was mailed to all the patients. One written reminder was mailed to the non-responders. Fifty-three patients (86%) returned the questionnaires. All patients with chronic fatigue (fatigue cases; n=18) were invited to a clinical examination and a cerebral MRI. Fifteen patients agreed to participate. Consequently 13 patients completed the examinations. Additionally, 14 aged-and gender matched HDS without fatigue was used as a comparison group yielding a total number of 27 patients participating in the study presented in Paper V.

Reference populations

1. Population data on Fatigue Questionnaire

The reference data on FQ is achieved from a population survey among the general Norwegian Population conducted in 1996.[83] A representative sample of 3500 Norwegian citizens, aged 19-80, randomly drawn from The National Register by the Norwegian Government Computer Centre (SDS), were mailed a questionnaire package. The package included FQ, items on sociodemgraphic variables and health variables. A total of 2323 (67%) people responded, and 2185 completed the questionnaires. Data from the population sample with the same age range as the patients included in the respective studies in this thesis were included as respective reference values.

2. Population data on EORTC QLQ-C30

A sample of 3000 people representative of the adult (above 18 years) Norwegian population was randomly drawn from The Office of the National Register. All participants received a mailed questionnaire package consisting of EORTC QLQ-C30, and form that covered sociodemographic data. A total of 1965 people completed the questionnaires, yielding a responsrate of 68%. Details to the survey is described elsewhere.[174] The results of this survey constitute the reference value on HRQoL from the general population, divided by age and

gender. Data from the population sample that were in the same age range as the patients included the respective studies were included as reference data in the different studies.

Design

This thesis constitutes three different types of studies:

1. Methodological study validating fatigue instruments (Paper I).
2. A prospective study with serial measurement of subjective health before, during and up to 3-5 years follows up (Paper II).
3. Cross sectional studies investigating possible etiology of fatigue (Paper III; IV; V).

1. The methodological study

In this study a fatigue scale in a HRQoL instrument, the EORTC QLQ-C30 fatigue scale, and a fatigue specific instrument, the FQ, were compared (Paper I). Two cohorts of patients, a cohort of patients with advanced metastatic cancer and a cohort of cancer survivors, were chosen in order to test the validity of EORTC QLQ-C30 fatigue scale in different types of patients with different symptom burden. Details to patient cohorts included are described elsewhere in the thesis. Patients who had completed both questionnaires according to the respective protocols were included. The patients with advanced cancer were included in a prospective study of HRQoL after palliative radiotherapy. Data at baseline, 12 and 28 weeks after intervention were used in the present work. This gives possibility to evaluate changes in symptom levels as the disease develops. The cancer survivors were originally included in a prospective study with the purpose to assess HRQoL, fatigue and psychological distress before, during and 3-5 years after stem cell transplant and high dose chemotherapy. In this work data from the assessment 3-5 years post treatment were included.

2. The prospective study

The prospective study was an extended follow up study of patients with leukemia or lymphoma treated with HDC and SCT/ASCT (SCT/ASCT patients respectively) or standard chemotherapy (CT patients) (Paper II). The patients were approached and completed the first

questionnaire prior to the transplant or start of standard treatment. Medical data were collected from the patients' records.

A questionnaire package was mailed to the transplant patients eight times and to the CT patients six times until one year after the transplant or start of chemotherapy. The last questionnaire package was sent to the patients as a cross sectional assessment 3-5 years after transplant or start of chemotherapy. At the last assessment, the FQ were added to the questionnaire package. Non responders received new questionnaires as a reminder after two weeks, including a statement coupon for indication of the reasons for withdrawal. The timeline for the assessment is presented in table 6.

Table 6. Administration of questionnaires in the prospective study

Assessment (months)	**Baseline**	**1 month pretrans-plant**	**2 weeks**	**1 month**	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	**3-5 years**
Interview	All									All
EORTC	All	SCT/ ASCT	SCT/ ASCT	All	All	All	All	All	All	All
HADS	All	SCT/ ASCT	SCT/ ASCT	All	All	All	All	All	All	All
FQ										All
Karnofsky WHO		SCT/ ASCT	SCT/ ASCT						SCT/ ASCT	

For practical reason the last assessment was performed as a cross-sectional assessment 3-5 years after transplant or start of chemotherapy. Ideally, we should have completed the longitudinal design with individual assessment 3 alternative 5 years after treatment.
In this study we assessed fatigue prospectively during the first year by EORTC QLQ-C30 fatigue scale. At the last assessment the FQ measuring physical and mental fatigue was administered to the patients. We would like to have baseline and prospectively assessed data from FQ. As this study was planned (1993), no Norwegian version of FQ existed, therefore we do not have prospectively data of FQ in this study.

3. Cross sectional studies

A cross sectional design was used in order to explore possible mechanism to fatigue. More specific, we wanted to explore to what extent fatigue can be explained by biological variables possibly related to the primary malignancy and/or treatment (Paper III, IV, and V).
Additionally to self-report questionnaires, objective examinations of certain organ systems were performed, and possible associations between subjective and objective health outcomes were explored. Details to outcomes and methods are described in the results part of the thesis.
The patient populations were previously treated for HD or NHL with a mean observation time since diagnosis of at least 6 years. Despite that we in only two of the studies defined a minimum time in complete remission of at least three years, the majority of the patients have had at least five years disease free survival indicating that they were cured of the malignant disease.

Methods

Patients self report questionnaires

Fatigue is measured by the Fatigue Questionnaire (FQ) and the fatigue subscale within the EORTC QLQ-C30. In consistency with the defined aims and hypothesis, HRQoL and psychological distress were additionally defined outcomes, and was measured in combination with the FQ in three of the five papers as listed in table 5.
Copies of all questionnaires are provided in the Appendix section at the end of the dissertation.

Fatigue Questionnaire

The Fatigue Questionnaire (FQ) was originally developed for assessing fatigue in patients with Chronic Fatigue Syndrome (CFS),[175] and was later refined in a validation study in which all items specifically related to CFS were removed.[78] It has good face validity and reasonable discriminant validity. It is found to be sensitive to change and allowed for detection of fatigue cases in epidemiological studies. In recent years it is employed in several studies in cancer populations.[4, 111, 135, 176] The FQ is translated into Norwegian, and Norwegian population norms have been published.[83]

FQ is a two-dimensional instrument, consisting of 11 items measuring physical fatigue (PF; 7 items) and mental fatigue (MF; 4 items) in two separate subscales. PF corresponds to the subjective feeling of being exhausted, lacking energy and less muscle strength. MF addresses the subjective experience of being mentally exhausted, and the items encompass concentration, memory and speech. Two additional items ask for the duration and extent of fatigue. The total sum of both subscales is designated total fatigue. Two scoring systems are employed. Likert scoring (0,1,2,3) is used for the construction of the sum scores for the subscales and the whole scale respectively. A higher score implies more fatigue. The dichotomised scoring (0,0,1,1) is only used for the case-definition. Based on the validation study, a case refers to a total dichotomised score of 4 or higher and duration 6 months or longer.[74, 78] The two factor structure was confirmed in the validation study (Paper I).

By missing data in four or fewer items, the missing value was replaced with the means of the corresponding known variable values from each sample.

EORTC QLQ-C30

EORTC QLQ-C30 is a health related quality of life questionnaire developed primarily for use in cancer patients.[62] The 30-item questionnaire is composed of scales that evaluate physical (5 items), emotional (4 items), cognitive (2 items), role (2 items) and social (2 items) function as well as general well being. Higher scores indicate better functioning. Three symptoms scales evaluate fatigue (3 items), pain (2 items) and nausea and vomiting (2 items), and 6 single items measure financial impact and various physical symptoms. Higher scores on these scales and items indicate more symptoms. Before statistical analyses are made, the raw scores are linearly transformed to a 0-100-point scale.[177]

Missing items were imputed according to the method advocated by the EORTC Quality of Life Study Group.[177] If at least half of the items from the scale were completed, the values of the missing ones were imputed as the mean value of the completed items.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is widely used for assessment of psychological distress in cancer patients.[178, 179] The Norwegian version of HADS was released in 1988. It contains 14 items, measuring anxiety (7 items) and depression (7 items) in two separate subscales. The responses are scored 0,1,2,3. The total score of each scale is derived by simple addition, and a higher score implies more distress. For anxiety and depression case detection, two cut-offs is recommended by the authors;[178] a mean score of eight to ten is defined as a probable case, and 11 or higher is defined as a definite case. The lower threshold was used in this study for the detection of possible cases.

Observer rated scale

Karnofsky Performance Status Scale

The Karnofsky Performance Status (KPS) scale is an observer rated scale, which is frequently referred to as a proxy measure of HRQoL in clinical trials. It has been used in validation studies of HRQoL measures.[62] The scale only measures physical function as one dimension of the HRQoL concept. It contains 11 categories ranging from normal performance (100%) to death (0%).

Clinical procedures

Laboratory analysis

Blood serum diagnostics were performed in the clinical studies described in paper III-IV.

Hormone analyses

Laboratory tests of serum levels of thyroxin stimulating hormone (TSH) and thyroxin hormone (FT4), follicle stimulating hormone (FSH), lutein hormone (LH), estradiol and testosterone was performed according to standard procedures. The thyroid and gonad function was classified according to standard values of the serum hormone levels as described in the papers.

Cytokine analyses

In Paper III, interleukin 6 (IL-6), tumour necrosis factor (TNF), and soluble TNF-p55 and p75 receptors were determined in serum samples from blood drawn into sterile vacuum tubes without additives. Tubes were immediately immersed in melting ice, and serum samples were stored at –70°C in multiple aliquots until analysis.

IL-6

IL-6 dependent mouse hybridoma cell line B13.29 clone B9 determined IL-6.[180] Serial dilutions of serum samples were incubated for 72 hours with IL-6 dependent cells. Viability

was measured in calometric assay with the MTT tetrazolium salt (Sigma Chemical Co, St. Louis, Missouri, USA).[181] Recombinant IL-6 was included as a standard.

TNF

TNF was determined by its cytotoxic effects on the fibrosarcoma cell line WEHI 164 clone. [182] Recombinant TNF was included as a standard.

Soluble TNF-receptors (sTNFR)

The TNF receptor p55 and p75 were analysed by immunoassay.[183] Immunoplates were coated with the monoclonal antibodies IV4E and 3H5, recognizing non-TNF binding sites of p55 and p75 TNFR, respectively. Recombinant human p55 and p75 (provided by Dr. Loetscher, F. Hoffmann-LaRoche, Basel, Switzerland) served as standard. Measurement of soluble TNF (sTNF) receptors bears some advantage compared to direct quantification of TNF. sTNF receptors are very stable, can be determined in stored sera, and allow some insight into TNF biology. Both receptors sTNFp55 and p75, as well as TNF are found to be elevated in cancer patients.[184, 185]

Immunological analysis of cerebrospinal fluid and serum (paper V)

In Paper V we performed immunological analysis of serum and cerebrospinal fluid of the patients with pathological brain MRI lesions.

Immunological analysis of cerebrospinal fluid

Spinal punctures were performed at L3-L4 or L2-L3 vertebral spaces using a 25G spinal needle. The spinal fluid was examined for cells, protein and glucose concentration. Protein electrophoresis was performed to analyse immunoglobulines. IgG isoelectric focusing was performed in order to improve the exposal of oligoclonale bands. An extended screening included anticardiolipin antibody IgG/IgM (diagnostic of systemic lupus erytematosus), concentration of lyzozymes and ACE (diagnostic of sarcoidosis of the central nervous system), and serologic analysis of Lues, Hepatitis B and Borrelia.

Immunological analysis of serum

Blood serum diagnostics were performed including analyses of glucosis, kobalamin and protein (protein electrophoresis with IgG isolecetric focusing). An extended screening included antinucelar antibodies (ANA), neutrophil cytoplasma antibody (c-ANCA (proteinase 3 / p-ANCA (myeloperoksidase)), anticardiolipin antibody IgG/IgM, serum concentration of lyzozymes and ACE, cryoglobulin, and serologic analysis of Lues, Hepatitis B and Borrelia.

Assessment of cardiopulmonary function

Evaluation of the cardiopulmonary function and possible relation to fatigue is described in paper IV. The assessment of cardiopulmonary function was performed at the Department of Thoracic Medicine and Medical Department, the National Hospital, University of Oslo in the frame of the doctoral thesis by Mai Brit Lund.[170] In the following a description of the procedures is given in accordance to the thesis by Lund. [170]

Assessment of pulmonary function

All measurements were performed with the Gould automated system 2400 (Sensormedics BV, Bilthoven, Netherlands). It is a computerized pulmonary function unit that provides following test capabilities: spirometry, lung subdivisions, and lung volume determination by the multibreath Helium equilibration method, and single breath diffusing capacity.

Measurements of ventilatory function

The measurements of ventilatory function included measurement of static lung volum by the multibreath helium equilibration method, and dynamic spirometry.

Measurements of gas diffusing capacity (TLCO)

The transfer factor for the lung for CO (TLCO) was measured by the single breath technique. The alveolar volume (VA) was calculated by the helium dilation method during the same manoeuvre. In all subjects the measured TLCO-values were also adjusted for the Hb-

concentrations obtained at the same day as the lung function testing. For the Hb-correction, the method of Cotes et al.[186] was used, which has been the method recommended by both the American Thoracic Society (ATC) and the European Respiratory Society (ERS).[187, 188] In the follow up study of HDS there was practically no difference between the measured and the Hb-adjusted TLCO values. The majority of the subjects were non-anaemic adults, and only in few cases did the Hb-adjusted TLCO values differ significantly for the measured values.

Reference values

Reference equations provide a context for evaluating the pulmonary function values of an individual subject or a study population in comparison to the distribution of measurements in a reference population.[170] The reference population and the study population should comprise of subjects with similar characteristics for the variables that affect lung function (sex, age, height, race). Additionally, specific methodological, epidemiological and statistical criteria should be fulfilled when selecting the reference values.[189] In the follow up study of HDS the reference values recommended by the ERS were applied [188, 190].

It is a common practice to express the results of pulmonary function testing as percent predicted, i.e values observed/value predicted x100, and to regard 80% of predicted as the lower limit of normal. In the study by Lund et al 80% of the predicted corresponded to the lower 5% percentile of the summary equations for lung volumes and TLCO in the reference materials recommended by the ERS.[170]

Radiographic evaluation

Chest radiographs in standard anteroposterior and left lateral projections were included in the assessment of pulmonary complications in the follow up study of HDS described in paper IV. The HDS included in the study had all received high-voltage chest radiation. Upper and medial parts of their lungs had been exposed to the entire radiation dose of 40-42 Gy, while the rest of the lung tissue had received scattered radiation or radiation transmitted through the lung shielding. It was therefore assumed that a proportion of the patients had developed various degrees of radiation fibrosis.[170]

The occurrence and degree of radiation fibrosis was described according to the method described by Jensen.[191] It is the only existing standardized and validated method for systematic radiographic evaluation of pulmonary fibrosis after mantle field radiation. According to this method, fibrosis was classified as “none”, slight”, “moderate”, or “severe” based upon a scoring system of the fibrotic manifestations. The radiographs were graded in blinded manner by two independent observers. In case of discrepancy, the radiographs were re-evaluated by the two observers jointly and an agreement was reached.

Assessment of cardiac function

Echocardiography

Transthoracic ultrasonic measurements were obtained by Vingmed CFM 700 or 750 cardiac ultrasound machine (Vingmed Sound, Horten, Norway) with a Duplex mechanical annual array probe. The probe applied the frequency 3.25 MHz for imaging tissue and 2.5 MHz for Doppler recordings.[170]

The subjects were examined in the lateral recumbent position after 15 minutes of rest. The heart was visualized using standard ultrasonic techniques and acoustic windows. M-mode echocardiography, two-dimensional technique and Doppler recordings determined cardiac dimensions and blood flow. Pulsed, continuous and colour Doppler echocardiography in at least three planes were used for exploring heart valve function. Two well-trained technicians did all the echocardiographic examinations, and the recordings were supervised and interpreted by the same senior cardiologist. However, as the observers were not blinded, some degree of observer bias cannot be excluded.

Exercise testing

The HDS included in the study described in Paper IV performed an exercise test. A stationary, electrically braked cycle ergometer (ErgoMetrics 900, Jaeger) was used. The initial workload was 50 watt, and increments of 50 watt were subsequently added every 4 minutes until exhaustion (defined as inability to pedal at 60 rev/min). The patients were monitored continuously by standard 12-lead ECG, and tracings were recorded at the end of each exercise step and every 2 minutes during the post-exercise recovery phase (minimum 5 minutes). A

pulse oximeter with a flexible finger probe (Minolta Pulsox-7, Devillbiss) was used for continuous monitoring of oxygen saturation.[170]

The major reason for the principal investigators for applying exercise test was to detect coronary artery disease, which is reported in patients previously treated with mediastinal radiation.[192-195] In non-malignant patients with coronary heart disease and heart insufficiency, fatigue is a prevalent symptom.[89] We therefore decided to include the exercise testing in the analyses of possible relationship between cardiac sequelae and fatigue. We also wanted to explore a possible relationship between fatigue and physical performance that in case of impaired physical performance indirectly could indicate the effect of cardiopulmonary dysfunction and fatigue. However, this was not in accordance to the aim of the principal investigators. For our purpose the major objective for this examination would have been to test exercise capacity. Such as test would include measurement of aerob capacity, peak oxygen uptake, gas exchange, and lung function including spirometry.

The MRI procedure

In the study described in Paper V, brain MRI examinations of HDS with and without fatigue were compared, in order to find possible explanatory factors to fatigue. The MRI examinations were performed on a 1.5-T MRI (Marconi Edge; Marconi, Cleveland, Ohio). The imaging protocol consisted of sagital T1-weighted images (TE/TR 12/240) and axial proton-weighted (TE/TR=16/3000), T2-weigthed (TR/TE=96/3000) and FLAIR –images (TE/TR=80/6433). Patients with pathological MRI-findings were reexaminated with MRI after 20-26 months in order to evaluate the stability of the findings. All images were analyzed independently by two radiologists, who were blinded to the identity of the patients.

Statistical analysis

Different statistical methods have been used in the different studies, and details are described properly in the respective papers. Standard descriptive statistics were employed to describe the distribution of fatigue, HRQoL and anxiety/depression scores at the different assessments. Differences in medical and demographic characteristics were tested by chi-square tests (nominal categorical variables) and two-sided t-test (independent sample) or Wilcoxon`s test (two-tailed) when appropriate (Paper II). Associations between fatigue and biological variables were tested by two-sided t-test (independent sample), Anova`s oneway analysis of variance, and chi-square statistics (nominal categorical variables). Bivariate associations were also analysed by Pearson`s correlation correspondingly Spearman`s rank test when appropriate. In Paper II and IV multiple comparisons forced a correction of p-value, and Bonferroni and Tukey were the correction methods applied.

Multiple regression analysis was used to detect relationship between fatigue and selected possible predictors as independent variables (Paper IV). Physical fatigue was included as the dependent variable in a linear regression model whereas fatigue cases (dichotomous variable) was selected as the dependent variable in a multiple logistic regression model. The selection of the independent variables was based on knowledge about possible predictors of fatigue in previous studies, and on results of the univariate analysis in the current study.

Different approaches were taken to evaluate the validity of the EORTC QLQ-C30 fatigue scale, FA (Paper I). Pearson's correlations were used to explore the relations between the FA and the FQ scales and single items (concurrent validity). Evidence of items convergent validity was defined as a correlation between one item and its own scale. Construct validity was evaluated by the use of principal factor with varimax rotation including all the fatigue items in the two questionnaires. The criteria for determining the number of factors were an eigenvalue above 1.0 and a visual inspection of the scree plot.

Clinical validity of the two measures, the extent to which the questionnaires scores are able to discriminate between subgroups of patients differing in terms of symptom burden or clinical status, was evaluated by use of two strategies: known groups comparisons and squared t – statistics.[61] The advanced cancer patients were dichotomised according to a selection of clinical variables. Student`s t-test for each instrument separately were used to examine

differences in fatigue between the dichotomised groups. The ratios of the squared t-statistics (t^2/t^2) were used to demonstrate the relative sensitivity of the two instruments. Since the FQ was regarded as the "gold standard", the t-statistics of the FQ were used as the denominator. In order to explore the measurement agreement between the two fatigue scales, fatigue scores measured by FA in relation to different fatigue levels measured by FQ were plotted.

Main results and summary of papers

Paper I

The validity of EORTC QLQ-C30 fatigue scale in advanced cancer patients and cancer survivors

In this paper the validity and the sensitivity of the fatigue scale in EORTC QLQ C30 were evaluated.

The EORTC QLQ-C30 is one of the most commonly used HRQoL questionnaire developed for use in cancer patients. The EORTC QLQ-C30 includes a three-item fatigue subscale, FA. It is limited knowledge about the validity, performance and sensitivity of FA as compared to a fatigue-specific instrument. The aim of the study was to validate the FA against the FQ, a two dimensional fatigue specific instrument which measure physical (PF, 7 items) and mental (MF, 4 items) and total fatigue (11 items).

The material included two different cohorts: A. Patients with advanced cancer included in a prospective randomized study of palliative radiotherapy (cohort 1, n=238). B. Patients with leukaemia and malignant lymphoma curatively treated with stem cell transplantation and HDC (cohort 2, n=128).

The FA correlated higher with the PF scale (r = 0.67-0.75) as compared to the MF scale (r=0.49-0.61) within the FQ. The item-scale correlations between the FA items and the PF scale were consistently higher than between the FA items and the MF scale. A factor analysis including all the items within the FA and the FQ identified two factors. All the FA items loaded on a physical fatigue factor (0.70-0.85). A floor/ceiling effect, indicating a high number of respondents with lowest, respectively highest scores, was observed more frequently in the FA as compared to the FQ. In the palliative care population a ceiling effect with highest possible scores was observed in 10.9% of the patients with the FA versus 2.9% with the PF in FQ. In cancer survivors a floor effect with lowest possible scores was observed for the FA in 24% of the patients versus 0% for the PF in FQ. In the palliative care population the PF discriminated better between diagnostic groups with different levels of fatigue than the FA did. A plot of fatigue measured by the FA against the PF illustrated a poor measurement agreement between the two scales indicating a poor ability of the scales to capture the same

patient population. These findings in addition to the floor/ceiling effects may indicate a suboptimal sensitivity of the FA.

In conclusion**,** the EORTC QLQ-C30 fatigue scale FA is measuring physical fatigue. A floor/ceiling effect seems to appear for the FA. The validity of the EORTC QLQ-C30 fatigue scale is to be questioned for use in palliative care patients. In studies with fatigue as an important endpoint, a domain specific instrument should therefore be added.

Paper II

A 3-5 years prospective study of health related quality of life, fatigue, anxiety and depression after stem cell transplantation

This paper present the result of a prospective study of fluctuations in HRQoL, fatigue and psychological distress during the course of HDC followed by allogeneic or autologous stem cell transplantation (SCT/ASCT) and during the periods of rehabilitation. A follow up to at least three years post treatment were conducted with the objective to explore fatigue in patients with haematological or lymphoid malignancy as a risk group of developing chronic fatigue documented by others.

The study populations were patients with leukaemia receiving allogeneic stem cell transplantation (SCT) and patients with malignant lymphoma receiving autologous stem cell transplantation (ASCT). Lymphoma patients receiving standard chemotherapy (CT), and data from general population were used as comparisons groups.

At baseline there were clinically significant differences across the two transplant groups in direction of better HRQoL in the SCT group. The differences in global QoL and fatigue were most pronounced in favour of the SCT group. At 1 year post treatment the SCT group reported significantly higher functional scores and less symptomatology as compared to ASCT and CT patients. This pattern remained stable at the assessment 3-5 years after treatment. The functional and symptom scores were mainly unchanged in all groups at 3-5 years follow up as compared to 1 year. All groups reported higher levels of fatigue as compared to the general population 3-5 years after treatment, however only in the ASCT

group a significantly higher level (28%) of chronic fatigue was found as compared to SCT group (11%) and norms (9%). The ASCT group reported additionally poorer role, cognitive and social function as compared to the norms. No differences were found in anxiety and depression between the treatment groups at baseline, 1 and 3-5 years after treatment or as compared to the norms.

In conclusion, the majority of the patients perform well after 3-5 years post treatment as found at 1 year assessment. The ASCT patients demonstrated poorer function and more symptoms as compared to SCT and CT group and as compare to general population. This study also confirmed previous studies reporting more fatigue in lymphoma patients and that it last for many years after treatment.

Paper III

High level of fatigue in lymphoma patients after high dose therapy

As highlighted in Paper II, medical late effects and secondary effects on subjective health like fatigue are of concern after HDC supported by stem cell transplantation. Changes in the endocrine system such as gonadal dysfunction and in the immune system are well known medical complication to autologous bone marrow transplantation (ABMT), but an association to high levels of fatigue has never been explored in these patients. This paper presents a cross sectional study of subjective health and possible underlying factors that might explain fatigue in patients with malignant lymphoma treated with HDC and ABMT. The patients population constituted 33 lymphoma survivors (median age 39 years), and observation time since ABMT were 4-10 years. The patients' scores were compared to general population norms.

Fatigue was highly prevalent compared to general population ($p<0.001$). Females reported significantly more physical ($p<0.01$) and total fatigue ($p<0.05$) as compared to males. Patients reported reduced function status and in particular reduced role, cognitive and social function and financial difficulties as compared to general population ($p<0.01$). Females demonstrate poorer HRQoL than males when compared to gender-specific references. Patients who were partly employed (=6) or not employed at all (n=8) were more fatigued than full-time employed (n=18) ($p<0.05$). No disease or treatment variables were significantly associated

with high levels of fatigue. The relationship between fatigue and endocrinological and immunological abnormalities were explored. Gonadal dysfunction was found in the majority of the patients, but no statistically significant endocrinological explanation of fatigue could be demonstrated. The levels of cytokines IL-6 and soluble receptors of TNF-p55 and TNF-p75 were slightly elevated and only a weak association was found to fatigue.

In conclusion, the high level of fatigue among female long-term survivors after ABMT may be related to the gonadal dysfunction, but further larger studies are needed to confirm such an association. Even though no clear association between cytokine level and fatigue was found, the effects of long term exposure of cytokines on central nervous system, on muscles, on endocrine system and finally fatigue, is of special interest to investigate further in cancer patients. The high level of fatigue among part-time and not employed patients is of major concern. Impaired role function is found to be associated with ability to work, and high levels of fatigue imply that returning to work might be problematic.

Paper IV

Late medical complications and fatigue in Hodgkin´s Disease Survivors

Late cardiopulmonal and thyroid complications are frequently reported and well documented in HDS. In this study we explored whether fatigue in patients treated for HD can be explained by cardiac, pulmonary and thyroid function after ended treatment.

Two dataset from the same cohort of patients were combined. Four-hundred and fifty-nine patients treated for HD at the NRH from 1971 to 1991 were included in a cross-sectional follow-up study of subjective health status including fatigue. A subcohort of HDS treated from 1980 to 1988 were included in a separate study in which long term cardiac, pulmonary and thyroid complications were assessed. Mean observation time since treatment was 9 (± 3) years. All patients had received radiotherapy, and 63 patients had received additional chemotherapy. The present study is comprised of the 92 patients (mean age 37 years, range 23-56) who participated in both studies.

Above one third of the patients (n=34) had pulmonary dysfunction. HDS with pulmonary dysfunction were more fatigued than HDS with normal pulmonary function ($p<0.05$). Gas transfer impairment was the most prevalent type of pulmonary dysfunction, and three times as many patients with gas transfer impairment reported chronic fatigue (duration 6 months or longer) compared to patients without pulmonary dysfunction (48% vs 17%, $p<0.01$). In a multivariate analysis gas transfer impairment was the only significant predictor of physical fatigue ($p=.01$) and of fatigue cases ($p=.002$). Approximately 50% of the patients had significant cardiac pathology, but they did not report more fatigue than HDS without cardiac sequelae. A trend in direction of more physical fatigue was observed among HDS with coronary artery disease (CAD, n=6) versus HDS without CAD (PF 12.7 VS 9.4, $p=.05$). Above 50% had thyroid dysfunction and one third were euthyreot, while 15 patients had hypothyroidism with replacement therapy. The latter groups reported more fatigue as compared to HDS with thyroid dysfunction ($p=.02$).

In conclusion, pulmonary dysfunction is associated with chronic fatigue in HDS. The lacking differences in fatigue level between HDS with and without cardiac pathology may be related to a possibly limited severity of the cardiac pathology. Both pulmonary and cardiac dysfunction due to late effects after cancer therapy are expected to progress in the course of time after therapy. HDS with hypothyroidism and replacement therapy reported more fatigued as compared to HDS with thyroid dysfunction. The response evaluation of replacement therapy of thyroid dysfunction after treatment for HD needs further investigation.

Paper V

Brain lesions in chronic fatigued survivors of Hodgkin´s Lymphoma - an explorative study

Fatigue is a predominant symptom in chronic inflammation and non-malignant diseases such as MS, systemic lupus erythematosus and chronic fatigue syndrome. Pathophysiological factors including brain abnormalities have been suggested as possible causes to fatigue in these cohorts of patients. The aim of this study was to investigate possible relationships between MRI brain lesions and fatigue in HDS. Fatigue was assessed in 53 adult patients treated for HD in the periode 1987 to 1997, without evidence of active disease in 1997.

Eighteen patients were classified as fatigued, and 13 of these patients were examined for the presence of MRI brain lesions. An age- and gender matched population of HDS without fatigue was included as a comparison group.

Two of the 13 HDS with fatigue had pronounced coalescent T2-hyperintense white matter lesions in both cerebral hemispheres, one had subtle T2-hyperintense white matter lesions and one had a cerebellar infarction. Two of the non-fatigued HDS had subtle punctuate white matter lesions in both cerebral hemispheres. Analysis of cerebrospinal fluid and blood serum in patients with brain MRI lesions did not confirm any relationship between examinations related to immunologic mechanisms and fatigue and/or MRI lesions.

Fatigue in HDS is a complex phenomenon. An association between cerebral white matter lesions and fatigue were found in the present study. Systemic effects of radiotherapy and chemotherapy, or brain tissues damage caused by the disease itself are possible explanations for these findings. This study calls for further studies of the causality for fatigue in HDS.

Discussion

Subjective outcomes or HRQoL is more often used in clinical studies today as compared to 10-20 years ago. New important findings are published with HRQoL as the main outcome, such as in palliative studies.[196-198] It is also used in studies aiming at life prolongation and curation as secondary outcome as well as in long term survivors after intensive curative treatment.[171]

In this thesis the overall aim is to improve the scientifically understanding of fatigue in lymphoma patients. The attempts to address possible etiological factors related to fatigue or to causes to fatigue in HDS may give empirical evidence for addressing some specific hypothesis in future studies.

As in research in general the validity of the subjective outcomes are of crucial importance. Two aspects of the validity of the EORTC QLQ C30 have been addressed, namely the dimensionality and the sensitivity of the fatigue scale within this QoL instrument.

One obvious reason to focus the work on the EORTC QLQ-C30 is the common use of this instrument in cancer research as well as in clinical practice. It was originally developed as a cancer specific instrument and validated in a general cancer population internationally,[62] and nationally.[199] These validation procedures have only to a limited extend compared the behaviour of the instrument in different populations directly and/or by using a domain specific instrument as a "criterion". Recently the EORTC QLQ-C30 was compared with the SF-36 in chronic non-malignant pain patients by our group.[200]

Fatigue assessment

A lack of consensus surrounds on how to assess fatigue. Since fatigue is a subjective phenomenon it is agreed that it should be measured by patients' self assessment. A number of fatigue instruments exist, both uni-dimensional and multidimensional.[64] All measurement, from blood pressure to HRQoL assessment including fatigue, should satisfy basic properties. These are validity, reliability, sensitivity and responsiveness. For subjective symptoms such as fatigue, which is not directly observable, or easily quantified, a need exist for reliable instruments that measure what it is intended to measure in different patient population, and instruments that is useful for its intended purpose.

Floor-ceiling estimates were used in this thesis to assess the sensitivity of FA, which is the instrument's ability to discriminate between patients with a very high and very low level of fatigue. It was shown that the instrument behaved differently between the palliative patients and the leukaemia/lymphoma survivors (Paper 1).[201] This finding indicates one of several challenges in the generalizability of validation studies. First of all, this indicicates that these aspects of validity ie "floor/ceiling effects" probably are cohort dependent phenomenon, which means that an often cited assumption in several validation studies ,"the instrument is found valid for use in cancer patients", should not necessarily be accepted as a general statement unless the validity have been evaluated in a series of cohorts. The findings in our study underline the importance of validating instruments in various cohorts with variations in frequency and intensity of symptoms, such as fatigue. The cohort dependent validity issues are rarely taken into consideration in instrument development as well as in the further critical evaluation of its use. The ideal HRQoL instrument should yield similar high level of validity independent upon cohorts. However, it is probably too much to expect, since most of the instruments have been specifically developed for specific types of distress and/or are disease specific symptoms. As a consequence of these assumptions, a general statement high degree of validity must be judged critically. For example, the different disease specific instruments, their development and validation procedure and the results should be carefully assessed before one decides to include a given instrument in a study.

As expected, the FA seems to measure primarily the physical dimension of fatigue in both cohorts. In other words, this finding is robust when comparing cohorts. It is important to be aware of, when interpretating the FA in the EORTC QLQ-C30, that only one dimension of fatigue is measured, which is rarely discussed in any detail, [62, 202 136, 176, 203] however the question about multidimensionality have also been addressed previously in relation to validation of the FA.[82]

This phenomenon points towards another challenge in outcomes interpretation namely the content of the scale or a measure. In general terms before deciding on a measure in a study, the researcher should carefully look into each question in a scale in order to understand the content of the measure. In other words one needs to carefully assess and judge the content on a detailed level and see how it fits with the research questions or hypothesis. Fatigue is in most patients considered to consist of two dimensions, physical and mental. Thus content as a

criterion, a summary scale of fatigue should measure both of the dimensions. The FA of the EORTC QLQ C30 measures only physical fatigue accordingly to our empirical data. By inspecting the content of the measure, the following items are included: “Did you need to rest?”, “Have you felt weak?” and “Were you tired?” This inspection would probably from most peoples perspective be in accordance with the empirical findings in our study. These findings also shed lights on one major challenge in symptom assessment in general and fatigue assessment specifically, the lack of any international consensus on how to measure fatigue in cancer care.

Another important finding in this study is related to the translation of single items from English to Norwegian. Both questionnaires have been translated according to international standards,[204] but still discrepancy was found. The English word “weak” which is found in one of the fatigue items in both FA and FQ is translated differently in the two instruments, namely as “slapp” (FA) and as “svak” (FQ). This finding underlines first the importance of standardised procedures and documentation of translation of questionnaire followed by a detailed validation of the language specific instruments, and ideally followed by retesting in ongoing empirical studies in the following years. Secondly, it is an argument to limit the number of instruments to be used in clinical studies. This will challenge the international research community to agree upon common standards, and ideally to develop new instruments in an international setting. By developing questionnaires in multi-language collaboration wording and phrases can be adapted up front to fit to the main type of languages involved in the development process.

A need for long term follow up

HRQoL is often measured in oncological studies today, either as a primary, secondary or even tertiary outcome. In palliative studies where symptom control and/or function improvement often are the primary aims, HRQoL and/or symptom checklists will be used to measure the primary outcomes, and survival and tumour response may be of less importance. On the other hand, in curative treatment cure rate and survival is considered in most studies to be the primary outcome, and quite often subjective symptoms, i.e. HRQoL to be of less importance.

During the last decade several follow-up studies have shown that the long term side effects of curative treatment is more pronounced than first expected.[205-209] Serious side effects have not

been detected earlier due to lack of prospective systematic follow-up of patients (http://odin.dep.no/repub/98-99/stprp/3). This might have happened because the focus during the 1980`s and 1990`s was to improve cure rate and survival while much less attention were given to a systematic follow up of possible treatment related side effects. Patients were primarily followed in order to detect relapse of the cancer disease. During the last decades more attention have been given to the need for systematic follow up and assessment of long term effects after curative treatment.[2, 206, 210-213]

In one of the studies in this thesis, a prospective follow-up design was chosen including a long term assessment 3-5 years after curative treatment were given (Paper II).[214] This study documented the value of following patients over time in order to better understand the pattern of subjective symptoms. The long term follow-up design detected a significant level of fatigue, particularly in the lymphoma patients as compared to leukaemia patients.

Another important argument for the need for long term follow up is the findings of reduced working ability in a small fraction of the ABMT cohort 4 to 10 years post treatment (Paper III).[215] Approximately half of the patients in the study were working part time or were unemployed. There were clinically and statistically significant differences in fatigue level in direction of more fatigue among lymphoma survivors being disabled as compared to those who were full-or part-time employed (Paper III).[215] This is in accordance with the few earlier studies of fatigued lymphoma survivors. In these studies it is reported reduced working ability,[107] more working difficulties among HDS as compared to survivors of testicular cancer,[69] and higher percentage of unemployment among HDS than the general population,[216] All these studies have in common a long follow-up time with range from 8-14 years since diagnosis.

Level of function

Despite a high level of fatigue and reduced working ability in subcohorts, the general impression is that patients who undergo high dose chemotherapy and stem cell support recover well after transplant. Overall QoL, level of function, ability to return to work are reported to be reasonably good in previous studies.[172, 217-221] Impaired physical functioning and increased fatigue are the main HRQoL domains that is reported to be of any clinical significans.[171, 219-225] Most studies included small cohorts without comparison groups, and had

a relatively short follow-up time, seldom beyond three months post transplant which may be considered as a limitation. Long term follow up of the function level several years after treatment should be assessed with a prospective design and repetitive measurements. To our knowledge, no prospective study has assessed fatigue with a longitudinal design beyond the first year after transplant.

In this thesis it is shown that the lymphoma survivors after ABMT or ASCT report impaired functioning and more symptoms as compared to general population (Paper II and III),[214, 215] and compared to leukaemia survivors (Paper II).[214] When data were broken down to age and gender and matched with general population, role and cognitive function as well as global QoL were more impaired in the ASCT patients 3-5 years post treatment as compared to the SCT patients (Paper II). [214] The longitudinal follow up confirm this pattern of persisting dysfunction among the ASCT patients in that these impairments were reported at baseline before transplant as well as 3-5 years post transplant in spite of improvements in other function scales during follow-up.

The findings in the lymphoma patients confirm a pattern of dysfunction as also indicated in the existing literature[69, 107, 216] Why lymphoma patients seem to be more affected than other cancer patients after treatment is probably multifactorial as discussed in this thesis.

Both the role and cognitive function impairments are of special concern for the patients. Impaired functions reported so many years after ending treatment could indicate a significant health problem. Role function has been particularly associated with ability to work. Studies have operationalized returning back to normal life as resumption of professional and private roles.[219, 221, 226, 227] Work-related problems, inability to resume social role, financial problems, worries about the future and fear of relapse are frequently reported problems among cancer survivors.[217, 225, 228-232] This pattern is retrieved in Paper III, even after 4-10 years post transplant approximately half of the patients were working part time or were unemployed. Financial difficulties was significantly more frequently reported among the lymphoma survivors after ABMT, as compared to general population (Paper III).[214, 215] Financial problems might be a natural consequence of the employment status, but may also reflect general difficulties with loan and insurance coverage for people with a history of cancer. Such issues were not of concern earlier when the curation rate of cancer were low, and is a reminder of the challenges that the long term effects may have on cancer survivors.[233]

Cognitive function is an important domain in HRQoL. Some of the most frequently assessed domains are concentration, memory and attention. Studies have reported that patients after chemotherapy complain of difficulties in thinking and memory.[53-57, 160, 223, 234, 235] Our studies demonstrate significantly impaired cognitive function longitudinal assessed in patients during and until 3-5 years post transplant (Paper II) [214]. Our cross sectional study of lymphoma survivors after ABMT demonstrated that cognitive function is impaired even up to 4-10 years after ABMT when compared to general population ($p<0.001$) (Paper III).[215] These findings are in accordance with the existing literature of cancer survivors after chemotherapy or transplant.

The assessment of cognitive function by mean of a self report HRQoL questionnaire have been critizised.[58, 236] By inspection, the two items of the cognitive function scale CF in the EORTC QLQ-C30 are identical with two of the four items of the mental fatigue scale (MF) in the FQ. A high item-by item correlation between the items in CF and MF indicated a strong correlation between these two scales (data not presented). This probably illustrate that similar phenomenon have different names in different instruments. Other types of methodology such as neuropsychological test should therefore be performed in further studies.

Why are some patients more fatigued than other?

There are probably several explanations to the inter-individual variability of fatigue. In order to investigate causality in general, a prospective design is preferable and the study samples need to be large enough. Before one possibly can embark on large scale studies, one should at least have "candidate" factors that may cause fatigue.

At the time our study was planned little knowledge existed on causes of fatigue. Therefore several variables were investigated. Associations, as shown in our studies are not any "prove" of a causal relation. For an association to be accepted as causal, certain criteria have to be fulfilled. First of all, the association should not be a result of coincidence. Furthermore it should not be a result of systematic error due to selection bias, assessment error or caused by any confounding variables.[237] According to B.Hill, the power of the association, (i.e. expressed by relative risk), consistent findings in several studies, cause and effect in the right order and the possibilities of biological comprehensibility are some main criteria of causality

while the only absolute criteria is the time relation between cause and effect.[238] Taken all these issues into consideration our studies should be regarded as hypothesis generating with regard to possible causality of fatigue in cancer disease survivors in general and in HDS specifically.

"Causes" to fatigue

Fatigue is a final common endpoint for several diseases and conditions, and will therefore be found in several populations with more or less impact on the patients` subjective experience of health. Pulmonary, cardiac and endocrine function was targeted in this thesis as "candidate" factors that may possible cause fatigue in patients treated for lymphoma . Late effects within these organs systems after treatment for both HD and NHL are common , and to our knowledge no study have investigated whether organ dysfunction can provide possible explanation to fatigue among survivors of HD and NHL.

Pulmonary dysfunction

In this thesis we found that pulmonary dysfunction in HDS treated with radiotherapy alone or in combination with chemotherapy was significantly related to increased fatigue (Paper IV).[239] No major associations were found between cardiac sequelae or endocrine dysfunction and fatigue in the cohort investigated. How valid are these finding? Some important aspects are to be commented upon to shed light on these findings.

The examinations of cardiopulmonary and endocrine function and of fatigue were performed at two different time periods. The cardiopulmonary and endocrine function was explored in 1993.[170] The assessment of fatigue was performed in 1994.[240] The observations were cross-sectional with a certain time difference between the assessments. The follow-up period is however long, and the time interval between the two assessments do probably not affect the results of the analyses. Despite the time interval, the study was not designed to assess pulmonary pathology that may cause fatigue. A cross sectional evaluation of the cardiopulmonary status offer only a picture of the situation now, and perform no additionally information of the situation before or the development of cardiopulmonary dysfunction and related symptoms over time. As we lack baseline information about fatigue, no objective evaluation of the cardiopulmonary function before start of the treatment for HD exits. It is however assumed that the cohort of HDS had a baseline normal lung function.[170] The cross

sectional design do not prove any causality, but generate a hypothesis that HDS develop pulmonary pathology also develop more fatigue. This hypothesis needs to be investigated in a prospective study with larger cohorts.

Fatigue is an unspecific symptom prevalent in several chronic conditions such as chronic pulmonary diseases, COPD, and chronic heart diseases, diseases inwhich also dyspnoe is a prominent symptom. In studies of COPD patients report they have difficulties to distinguish between fatigue and dyspnoe.[241] Fatigue and dyspnoe may occure at the same or at different times in different patients but may be symptoms of the same disease. Therefore, there is a possibility that our assessment of fatigue have included patients with a subjective experience of dyspnoe more than fatigue, mainly due to the general uspesific characteristics of fatigue more than to insufficient methods of assessments.

We can however not exclude that the findings in our study indicate that there is a causal relationship between pulmonary dysfunction and fatigue. Lung fibrosis is one of the most frequent chronic pulmonary complications after radiation therapy and is a major factor in the development of gas transfer impairments. Lung fibrosis was found in 76% of the HDS with gas transfer impairments in our study. The cardinal symptoms of lung fibrosis is dyspnoe. The arterial oxygen desaturation following pulmonary abnormalities may lead to more dyspnoe during activity, which again result in avoidance of activity and finally lead the patients into a negative circle with further decondition as a result. Studies from HDS as well as from patients with COPD have shown that dyspnoe is the exercise limiting symptom.[242, 243] Dyspnoe in excertion was also reported by almost one third of the patients investigated in our study and most pronounced among HDS treated with both radio- and chemotherapy (Paper IV).[239] Reports of positive relationship between exercise related improved oxygen use and improved fatigue/dyspnoea support this assumption.[152, 153]

Cardiac dysfunction

Cardiac pathology did not explain fatigue in the HDS investigated in our study. However, higher level of fatigue was found among patients with coronary artery disease (CAD) as compared to those without CAD. Minor severity of the cardiac pathology and short observation time may be some reasons for the lack of a possible association between cardiac pathology and fatigue. A longer observation time would probably uncover increased number of patients with cardiac pathology, on the other hand will longer follow up periode also

weaken the relationship between disease, treatment and symptoms of fatigue. One need to take into consideration also a “natural” non cancer related development of cardiovascular disease as the population are getting older in long term follow up studies.

Several studies have evaluated cardiovascular status on long-term survivors treated with chest radiotherapy in various populations in terms of age, diagnosis and/or treatment.[195, 244-246]. In a recent study with multiple screening of HDS 6-27 years since diagnosis, a serial of unexpected, clinically significant cardiovascular abnormalities were discovered although the patients were asymptomatic and reported their overall health as good.[247] The endothel injury from radiation therapy is first of all a progressive injury which will develop atherosclerosis and coronary arterty disease over time. First then the injury will be symptomatic for the patients. The subcohort with symptomatic CAD in our cohort is small, and may possibly be due to short observation time. The results of several studies undertaken in the 1980 aiming to assess risk of CAD after mediastinal radiation therapy have been inconclusive.[195, 248-250] However, analyses have subsequently shown a clearly increased risk for CAD and myocardial infarction after mediastinal radiation therapy for HD.[248, 251, 252] Fatigue is a cardinal symptom in patients with chronic heart diseases, and with negative effects on physical activity and quality of life.[253] Therefore, cardiovascular status should be followed in patiens treated for HD and NHL to capture when these subclinical findings developen clinical manifestation. In further studies cardiovascular pathology and specifically CAD should be considered as candidates to explain fatigue or as one of several possible causal factors.

Endocrine dysfunction

The weak association between fatigue and thyroid function in HDS needs further investigation. The sample sizes in our study were small, the majority of the HDS had thyroid dysfunction or were substituted for hypothyroidism. Hypothyroidism develops gradually, and the cross sectional design is not an appropriate design to test the association between symptom and disease. The documentation of clinical and biochemical effects of substitution therapy for hypothyroisis and other endocrine dysfunctions in HDS is sparse, and the evaluation of treatment effects upon symptoms is unclear. The endocrine system is complex and difficult to evaluate. Diurnal variation, physical and psychological factors influence the hormone levels. A prospective evaluation of fatigue and thyroid function in order to investigate the relationship between biochemical hypothyrosis and fatigue would be a

preferable design to evaluate this relationship. The next would be to perform a clinical controlled intervention study in well defined cohorts with fatigue as primary endpoint in order to evaluate the effects of substitution therapy.

The gender differences in fatigue among lymphoma survivors after ABMT as was demonstrated in paper III may be explained by the female gonadal toxicity or other unknown gender related factors.[215] The female lymphoma survivors after ABMT reported significantly more fatigue as compared to males. The literature of gonadal dysfunction and related symptoms after curative cancer treatment is scarce, and consequently it is difficult to conclude about the relationship between fatigue, gender and hormonal dysfunction. The endocrine hypothesis in relation to fatigue is therefore insufficient explored, and a thorough investigation of the HPA axis in lymphoma survivor should be performed.

Immunological abberations and brain lesions

In the literature several reports have discussed that fatigue in general[122, 155] as well as in HDS [113] is associated with high levels of cytokines. The specific cellular morphology of HD and NHL may result in high level of cytokines, and therefore it seems relevant to investigate this relationship. Whether the cytokine levels are elevated also in HDS several years after treatment is unclear. We selected the cytokines on the basis of previous research in this field, and the assessment was conducted in order to explore whether fatigue is associated with high levels of cytokines in HDS and NHL survivors. We did not capture any abnormalities in cytokines levels. Due to the cross sectional design of this study no baseline estimates of cytokines were available. This is a weakness of this kind of design and it is obvious that prospective design should be chosen also in this setting.

It has been speculated whether fatigue can be associated with minor brain lesions.[254, 255] MRI has been used in other patient population exploring fatigue in patients with cerebral pathology.[88, 113, 164, 254, 256, 257] In our study two of the 13 HDS with fatigue had pronounced coalescent T2-hyperintense white matter lesions (WML) in both cerebral hemispheres, one had subtle T2-hyperintense WML and one had a cerebellar infarction (Paper V). Two of the non-fatigued HDS had subtle punctuate WML in both cerebral hemispheres. These results are difficult to interpret as a possible etiologic explanation for fatigue in these patients. Cerebral

WML were found in both group of the HDS with or without fatigue, and express possible more a pathologic finding in the brain possible due to systemic effect of disease of HD or the treatment as it explain the fatigue experienced by these patients. A recent study could demonstrate specific alteration in activity of frontal cortex, cerebellum and basal ganglia in breast cancer survivors documented by functional neuroimaging 5-10 years after chemotherapy indicating a negatively impact on cognitive function due to cerebral effect of chemotherapy. To relate cerebral pathological findings to fatigue is challenging. It may depend on the localisation of the findings, and the direct and indirect effect of the lesions on mental or physical function. Which clinical manifestations are to be expected, and which cerebral lesions may explain or contribute to fatigue? As in other cross-sectional studies, we did not have any information about the patients` brain MRI before this examination performed as a part in our study. It may therefore be a weakness of this part of the study only to use the brain MRI to discover cerebral lesions that might explain fatigue. Complementary examinations such as neuropsychological tests could have been considered.[55, 258] Secondly, a prospective study of patients with HD that included baseline cerebral MRI and assessment of fatigue before and after treatment would have been a more superior design.

Conclusion

The results from this thesis can be summarised as follows:

- This thesis have demonstrated that the EORTC QLQ C 30 fatigue scale, FA, is one-dimensional measuring physical fatigue.

- Poor sensitivity of the FA in the EORTC QLQ C30 was found with major floor/ceiling effects and a poor ability to differentiate between diagnostic groups with different levels of fatigue.

- Fatigue and dypnoe is more frequent among lymphoma patients as compared to leukaemia patients 3-5 years after high dose chemotherapy and stem cell transplantation, and as compared to lymphoma patients treated with standard

treatment. Lymphoma patients report significantly more fatigue up to 10 years after transplant as compared to the general population.

- The lymphoma patients report clinical and statistical significantly impaired social, role and cognitive functions as well as poor QoL 3-5 years after transplant when compared with leukaemia patients after transplant and with lymphoma patients after standard treatment. These function scores were significantly lower as compared to the scores from the general population as well.

- Fatigue in HDS treated with mantle field radiotherapy (85/92 patients) alone or in combination with chemotherapy was associated with pulmonary dysfunction. Gas transfer impairment was a significant predictor of physical fatigue and of chronic fatigue among the HDS.

- A higher level of fatigue was found among HDS with coronary artery disease (CAD) as compared to patients without CAD. No other cardiac sequelae in the HDS investigated in our study were associated with fatigue in this cohort. In further studies cardiovascular pathology and specifically CAD should be considered as candidates to explain fatigue or as one of several possible causal factors.

- Endocrine complications such as gonadal dysfunction and hypothyrosis were weakly associated with fatigue in lymphoma survivors. We still consider that late effects in the endocrine system may possibly be of clinical importance in cancer survivors in general and above all in lymphoma survivors after both transplant and standard treatment.

- Fatigue in HDS is difficult to be explained by the MRI abnormalities presented as cerebral whiter matter lesion (WML) found in these patients, mostly due to few findings and the small sample size.

- In HDS with fatigue and cerebral WML no clinical or biochemical indicators of immune dysfunction were found. No differences in levels of proinflammatory

cytokines IL6 and soluble TNF-α receptors between lymphoma patients post transplant and age-and gender adjusted population values were found.

- The clinical consequence of WML lesions will possibly be related to the localisation and the severity of the lesions. Cognitive impairment or mental fatigue in cancer survivors is associated with WML as systemic effects of radiotherapy or chemotherapy or the disease itself. With such small sample size and the lack of baseline information of WML pre-treatment, a causal relationship to fatigue is therefore difficult to evaluate.

Future research

With more than 50% of cancer patients surviving more than five years beyond diagnosis, oncologists are challenged to expand their focus from acute care to managing the long-term health consequences of cancer. Cancer survivors are at increased risk for several late and long-term effects of cancer and other comorbid conditions, and many also seek lifestyle change to reduce dysfunction and improve long-term health. The survivors fear of recurrence and the fact that many survivors may not be aware of potensial late effects is also critical for an improved survivorship care. Survivorship research should include clinical epidemiological research aimed at physiological and psychological aspects of cancer survivorship and gain knowledge about follow up, intervention and surveillance strategies.

Based upon the studies in this thesis and new literature there are some issues to be raised with regard to future research. The main areas are: Assessment of fatigue and other relevant symptoms in prospectively designed studies, long-term follow up studies of fatigue, assessment of potential mechanisms for fatigue, and the clinical use of research findings.

Assessment of fatigue

It is an ongoing debate on how to improve the methods for assessment of functioning and subjective symptoms in cancer patients. With increasing interest to test interventions for fatigue and other bothersome symptoms it should be assessed in a clinical setting and this will require accuracy and efficiency.[259] Computerized adaptive testing (CAT) enables precise assessment of fatigue without administration of a large amount of questions that the patients have to answer, and should be developed as a comprehensive tool both for use in daily clinic and in research.

Longitudinal studies of fatigue

Trajectory of fatigue during cancer treatment and knowledge about persistent fatigue after cancer treatment is critical for an accurate understanding of post treatment fatigue. Prospective study design should be chosen, preferably including pre-treatment data. This design has three major advantages: The baseline values of fatigue will give more accurately the estimates of chronic fatigue corrected for baseline values during and after treatment. This design may uncover different trajectories of fatigue and possible risk factors for developing fatigue. Still there are few studies with a follow up beyond 5 years. Due to the adverse effects of fatigue future research should include evaluation of symptom burden, functional and employment status, and physical and emotional well being in the growing population of cancer survivors.

Long term follow up studies

Long term follow up is of particular important to detect late effects of cardiac and pulmonary dysfunction. Organ failure may develop wih time and worsen the functions as the patients get older. The Cancer Registry of Norway holds a complete database of all cancer cases systematically collected by requiring information from the clinicians and the pathologists.[1] By matching the data with the Register of Deaths at Statistics of Norway the mortality can be investigated. It is proposed that the mortality have changed in direction of increased non-cancer related mortality as compared to the cancer-related mortality. If so, the treatment has to improve with the aim to reduce the non-cancer related mortality. Research on late effects based on such matching is sparse in the existing literature, and presumably because few countries have national cancer and death registers.

Causes of fatigue after cancer treatment

Future studie should include more comprehensive assessment of potential mechanisms of fatigue after cancer treatment. Fatigue is probably caused by multiple factors which may differ for different patients. Possible mechanisms within the cardiopulmonary and endocrine system have rarely been investigated earlier like in this thesis, and need further investigation above all in frame of longitudinal and long term follow up studies. Promising mechanisms have also been identified within the immune and neuroendocrine system, supporting the hypothesis that inflammatory alterations underly mechanism for persisting fatigue. More extensive measurements of the inflammatory signaling activity in ordre to identify immunological biomarkers for post treatment fatigue is in focus, and need to be performed in different diagnostic groups of cancer survivors with persistent unexplained fatigue.

As a final comment, the physicians generally underestimate the level of fatigue and its impact on patients HRQoL and functioning. This statement is based on both scientific documentation and from clinical experience.[260, 261] The fact that the physicians believed pain to be more debilitating than fatigue, may concern the physician trend to give attention to symptoms that more easily can be treated. Few treatment options do exist that quickly relieves fatigue, and thus the willingness to discuss fatigue with the patients may be low. It is important to be aware of that patients often associate fatigue with active disease and may misinterpret fatigue as a symptom of relapse. Therefore, it is important to improve the understanding of fatigue as a subjective phenomenon.

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Erratum

Paper I

Paper I is not included due to copyright.

Paper II

Paper II is not included due to copyright.

Paper III

Original Article

High Level of Fatigue in Lymphoma Patients Treated With High Dose Therapy

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Abstract

With the success of high dose therapy supported by autologous bone marrow transplantation (ABMT) for malignant lymphomas, medical late-effects and secondary effects on subjective health, like fatigue, are of concern. Fatigue is poorly understood and correlates have been barely addressed. Health-related quality of life (HRQL), fatigue, and correlates to fatigue, including endocrinological status and serum levels of interleukin-6, tumor necrosis factor, and soluble tumor necrosis factor receptors, were investigated in a cross-sectional study of 33 lymphoma patients (median age 39 years) 4–10 years after ABMT. The survivors were compared to general population norms. Fatigue was highly prevalent, and females reported significantly more fatigue and impaired HRQL compared to males and the normal population. Gonadal dysfunction was found in the majority of the patients, but no statistically significant endocrinological or immunological associations with fatigue could be demonstrated. The high level of fatigue among female long-term survivors after ABMT may be related to the gonadal dysfunction, but further studies of possible mechanisms behind fatigue are necessary. J Pain Symptom Manage 2000;19:446–456. *© U.S. Cancer Pain Relief Committee, 2000.*

Key Words

Fatigue, cancer, quality of life, high dose therapy, autologous bone marrow transplantation, cytokines, sex hormones

Introduction

High-dose therapy supported by allogenic or autologous bone marrow transplantation (ABMT) or peripheral progenitor cells support has rapidly gained acceptance as a curative treatment option for a number of cancers like leukemia and lymphoma. From being a highly experimental procedure, only given in advanced stages of malignant diseases, the utility of high dose therapy with allogenic and autologous stem cell support has expanded during the last several years,[1–3] leading to an increasing number of long-term survivors. These therapies are generally performed in young patients with long life expectancy. Despite the clinical suc-

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Accepted for publication: July 14, 1999.

0885-3924/00/$–see front matter
PII S0885-3924(00)00144-5

cess achieved with this treatment, the long-term toxic effects are of concern .[1–8]

Mortality and somatic-related morbidity have been the main outcomes in the clinical investigations after high dose therapy with stem cell support. During recent years, however, attention has been directed towards health-related quality of life (HRQL) as an endpoint after such treatment.[5–8]

HRQL is defined as a multidimensional concept consisting of physical, psychological and social dimensions.[9] Fatigue or vitality is a subdomain of HRQL, and is included in most HRQL-instruments. Fatigue is usually defined as a subjective phenomenon, and in the absence of objective measures, measurements of fatigue rely on subjective reports from patients themselves.[10] Patients in several follow-up studies after BMT report their HRQL as rather good.[8] However, deficits in specific domains in HRQL are frequently reported.[8,11] Fatigue was one of the three most frequently reported current problems in a study of 125 adult long-term survivors (6–18 years) of BMT/ABMT.[12] In a study of 29 adults 1–8 years after BMT, 76% reported "feeling tired".[13] Further, 50% reported fatigue and reduced energy level in a study of 24 adults 12–38 months post-BMT.[14] The majority of these studies may be regarded as inconclusive with regard to fatigue because specifically designed instruments assessing fatigue were not employed. Measuring fatigue by single items generally have poor reliability, and a large number of patients are required in order to detect quite modest changes of fatigue level. During recent years, specific fatigue instruments have been developed, and these instruments are preferred in clinical research.[15]

Fatigue is also a prevalent symptom in the general population; prevalence rates between 11% to 45% have been reported. In a randomized survey in the Norwegian population, 11% were classified as fatigue cases using the Fatigue Questionnaire (FQ).[16] Interpretation of fatigue data among cancer survivors without accounting for the high prevalence in the normal population might invalidate the conclusions. In a recent study of 459 Hodgkin's disease survivors (HDS) 12 years post treatment, the FQ was used. In this cohort, more than twice as many HDS (26%) were fatigued as compared to the normal population (11%).[17]

The pathogeneses of fatigue remain uncertain. Several somatic conditions, such as permanent changes in the endocrine or immune systems, hematological changes, neurologic impairments, or reduced heart and/or lung function, may cause fatigue.[18] To our knowledge, no one has investigated biological correlates of persisting fatigue among long-term cancer survivors.[19] The possible biological changes may either be related to the malignant disease itself or to the side effects from the treatment. In some studies, fatigue has been found to be associated with increased levels of the cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF).[20–22] Due to the presence of cytokines in the brain, it has been postulated that they might modulate neural function, as they are modulators of the immune system.[23] Endocrine causes of cancer-related fatigue also have not been properly investigated. Although gonadal dysfunction is a well-known medical complication of ABMT,[24] it has never been correlated with fatigue. Low testosterone levels in patients with advanced cancer are found to be common,[25,26] but an association with fatigue has never been investigated.

The primary aim of this study was to assess the prevalence of fatigue and HRQL in patients treated with high dose therapy and ABMT, and to compare these patients with norms from the general population. Furthermore, we wanted to explore the relationship between fatigue and disease and treatment variables, levels of cytokines, and endocrine abnormalities.

Methods

Patients

From 1987 until 1993, all 85 cases of malignant lymphomas requiring ABMT in Norway were treated at the Norwegian Radium Hospital. In January 1997, 46 patients were alive, in complete remission (CR), and invited by mail to participate in this study. Few studies on late side effects more than 3 years after ABMT exist[5] and we decided that a follow-up period of 3 years or more was appropriate to assess late side effects. One patient refused to see a new doctor, another answered too late for inclusion, and one had moved abroad. Four patients did not answer. Thirty-eight of the re-

maining 39 patients completed the mailed questionnaires. Before the clinical work-up, three patients declined to participate due to hospitalization (because of cerebral insult, myelodysplastic syndrome, and major psychiatric problems, respectively). Two of the blood samples were damaged during transportation. Thirty-three serum samples were valid for use. Of 38 patients who returned the questionnaires, the questionnaires from those 33 patients with valid serum tests were chosen. Of those 33 patients, 32 completed the entire quality of life questionnaire and all 33 completed the entire Fatigue Questionnaire.

Median age at study was 39 years, with a median observation time since diagnosis of 8 years. Median time since ABMT was 6 years (Table 1). The majority of the patients were in stage IVA. Sixteen patients with Burkitts lymphoma or lymphoblastic lymphoma received ABMT as a part of the primary treatment after a first remission. The remaining 17 patients with intermediate grade NHL, low grade NHL, or Hodgkin's disease received high dose therapy after a second or later remission. It was decided to divide the patients into two groups according to these criteria when assessing the relationship between diagnosis and treatment to fatigue. All patients received combination chemotherapy according to standard treatment protocols as part of the induction procedure before the high dose regimen, or as primary treatment alone. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the most frequently used chemotherapy regimen, as primary treatment alone, or in combination with high dose methotrexate as part of the preparation procedure. Fourteen of those 16 patients who were treated with high dose chemotherapy in first remission received high dose methotrexate as part of the induction therapy, and eight of them also received methotrexate intrathecally. Cyclophosphamide and total body irradiation (TBI) was applied as high dose therapy in 29 patients, and vepecid, cyclophosphamide, cytosar, BCNU (BEAC) in 4 patients.

Measures

A questionnaire was mailed to the patients. Non-responders were reminded once through a telephone call after one week. The questionnaire contained the following measures:

Fatigue Questionnaire (FQ). The Fatigue Questionnaire is an instrument specifically designed for assessing fatigue. It was developed for a hospital study of Chronic Fatigue Syndrome (CFS),[27] and was later refined in a validation study in which all items specifically related to CFS were removed.[15] Later, it was used in several epidemiological studies.[16] FQ is a two-dimensional instrument, consisting of 11 items measuring physical and mental fatigue. Additionally, two items ask about the duration and extent of fatigue symptoms. Each item has four response categories, scored 0, 1, 2, 3. Total fatigue (TF, all items) (range 0–33), physical fatigue (PF, seven items) (range 0–21) and mental fatigue (MF, four items) (range 0–12) are the sums of the scores for the whole scale or the physical and mental subscale, respectively.

The reliability of FQ was assessed by estimates of internal consistencies of the questionnaire. Cronbach's alpha scores were 0.92 (PF), 0.84 (MF) and 0.89 (TF), confirming the findings of previous validation study.[15]

European Organization for Research and Therapy of Cancer (EORTC) QLQ-C30. EORTC QLQ-C30 was used to measure HRQL.[9] The instrument consists of six functional scales that measure physical, role, cognitive, social, and emotional function, as well as overall Quality of Life. Three symptom scales measure fatigue, pain, and emesis, and six single items measure appetite loss, sleep disturbance, dyspnea, diarrhea, constipation, and financial impact.

All the scales and item scores were linearly transformed to 0–100 point scales.[28] For the functional scales and global health/Quality of Life scale, higher score represents better functioning and quality of life. Higher scores on the symptom scales correspond to more symptoms.

In two previous studies norms for the FQ and EORTC QLQ-C30 had been established from two random surveys of the Norwegian population.[16,29] Significant differences in the norms according to age and gender were found.[16,29] A decline in physical functioning and more symptoms were found with increased age.[29] The prevalence and level of fatigue increased with increasing age,[16] and women reported worse HRQL and more fatigue than

Table 1
Patient Characteristics (n = 33)

	n (%)
Age at time of study (yrs)	39 (18-59)[a]
Age at time of ABMT (yrs)	35 (15-55)[a]
Gender	
Male	18 (55)
Female	15 (45)
Years after diagnosis	
3–6	12 (36)
7–10	20 (61)
15–20	1 (3)
Years after high dose chemotherapy	
4–6	24 (73)
7–10	9 (27)
Diagnosis	
NHL, high grade, 1. remission (Burkitts lymphoma/Lymphoblastic lymphoma)	16 (49)
NHL, intermediate/low grade /HD 2. or later remission	17 (51)
Clinical stage[b] (n = 30)	
I	6 (20)
II	3 (10)
III	7 (23)
IV	14 (47)
Substage (n = 29)	
A	17 (52)
B	12 (36)
High dose regimen	
Cyclophosphamide and TBI	29 (88)
BEAC	4 (12)

[a] Median (range)
[b] At time of diagnosis according to Ann Arbor classification.
HD Hodgkins disease NHL Non Hodgkins Lymphoma.

men did. Due to the age and gender differences, an adjustment for these variables was performed. Responders in the older age groups, above 60 years, were deleted from the norms in order to match the ABMT sample, and a gender-specific stratified analysis was performed.

Sociodemographics, diagnosis, stage, histology, and treatment were based on the patients records and on the personal interview.

Blood Sampling Protocol

Interleukin 6 (IL-6), TNF and soluble TNF-p55 and p75 receptor values were determined in serum samples from blood drawn into sterile vacuum tubes without additives. Tubes were immediately immersed in melting ice, and serum samples were stored at −70°C in multiple aliquots until analysis. Serum samples for cytokine analysis were frozen and thawed only once.

Measurement of IL-6. IL-6 was determined by the IL-6 dependent mouse hybridoma cell line B13.29 clone B9.[30] Serial dilutions of serum samples were incubated for 72 hours with IL-6 dependent cells. Viability was measured in a calorimetric assay with the MTT tetrazolium salt (Sigma Chemical Co, St. Louis, Missouri, USA).[31] Recombinant IL-6 was included as a standard. We preferred the measurement of IL-6 instead of IL-1 since IL-6 is very stable, and like IL-1, reflects an immune activation.

Measurement of TNF. TNF was determined by its cytotoxic effect on the fibrosarcoma cell line WEHI 164 clone.[32] Recombinant TNF was included as a standard.

Immunoassays for detection of soluble TNF receptors (sTNFR) in serum. The TNF receptors p55 and p75 were analyzed by immunoassay.[33] Immunoplates were coated with the monoclonal antibodies IV4E and 3H5, recognizing non-TNF binding sites of p55 and p75 TNFR, respectively. Recombinant human p55 and p75 (provided by Dr. H. Loetscher, F.Hoffmann-La Roche, Basel, Switzerland) served as standard. Measurement of soluble TNR receptors bear

some advantage compared to direct quantification of TNF. sTNR are very stable, can be determined in stored sera, and allow some insight into TNF biology. Both receptors sTNF p55 and p75, as well as TNF, are found to be elevated in cancer patients.[37,38]

As reference group for IL-6 and sTNFR p55 and p75, serum samples from 10 healthy individuals were used. The reference population was selected in accordance to age and gender distribution in the patient sample.

Statistical Analysis

Bivariate associations were studied by χ^2 statistics (nominal categorical variables), two-tailed *t*-test (independent samples), or Pearsons correlation where appropriate. Differences in cytokines and cytokines receptor levels between groups were tested by non-parametric tests. Wilcoxon rank sum test (two-tailed) was used for comparison of the two groups; the Kruskal-Wallis test was used when $>$ 2 groups were compared. The correlation coefficients (r) were calculated using Spearman's rank test. A p-value of 0.05 was chosen to indicate statistical significance. In the analyses of the EORTC QLQ-C30, a difference above 10 is considered clinically significant,[29,34] while 7–10 might be considered as questionably significant. In order to interpret differences in mean estimates of fatigue, a comparison with general population scores might be used. In a previous study, we have reported mean differences between subcohorts of the general population.[16] By comparing the most healthy subcohort with those with poorest health, differences of 3.0, 2.6, and 0.4 were found for TF, PF, and MF, respectively.

Results

Fatigue

Patients cured of malignant lymphoma were significantly more fatigued than the Norwegian reference population (Table 2). The difference was most prevalent for physical fatigue. The mean total fatigue score (TF) was 17.9 and 12.8 among the women and men, respectively (p = 0.02). A similar pattern was found for physical fatigue (p = 0.01), whereas small differences between the genders were found in mental fatigue. Women reported significantly more physical fatigue and total fatigue as compared to the reference population. For the male population, no differences were found between patients and reference population. Tumor stage or substage at time of diagnosis was not associated with fatigue, nor was observation time since treatment or the treatment burden. Patients treated with high dose chemotherapy during the second or later remission who were exposed to a considerable treatment burden did not report significantly more fatigue than patients treated during the first remission (PF 8.7 vs. 11.3; TF 13.4 vs. 16.9, p = 0.10). A trend was observed, however, among women. Those treated with high dose chemotherapy during the first remission reported more physical and total fatigue than those treated during later remissions (PF 14.1 vs. 9.7; TF 20.8 vs. 14.7; p = 0.05 and p = 0.07 respectively). The majority (14 of 16 patients) of these patients received high dose methotrex-

Table 2
Fatigue in Patients and in Reference Population

	Females		Males		Total	
Fatigue	Patients Mean (95% CI)	Reference Population Mean (95% CI)	Patients Mean (95% CI)	Reference Population Mean (95% CI)	All patients Mean (95% CI)	Reference Population Mean (95% CI)
Physical	12.1[a,b] (9.6–14.5)	8.0[a] (7.8–8.2)	8.2[b] (6.3–10.0)	7.4 (7.2–7.6)	9.9[c] (8.4–11.5)	7.7[c] (7.6–7.8)
Mental	5.9 [a](4.6–7.2)	4.3[a] (4.2–4.4)	4.6 (3.5–5.7)	4.3 (4.2–4.3)	5.2[c] (4.4–6.0)	4.3[c] (4.2–4.4)
Total	17.9[a,c] (14.4–21.5)	12.3[a] (12.1–12.6)	12.8[c] (10.0–15.5)	11.6 (11.3–11.9)	15.1[a] (12.9–17.4)	12.0[a] (11.8–12.2)
n	15	921	18	874	33	1786

[a] $p < 0.001$ for differences in mean scores between patients and reference population.
[b] $p < 0.01$ for differences in mean scores between gender.
[c] $p < 0.05$ for differences in mean scores between gender, and between patients and reference population.

ate, and eight of them also received methotrexate intrathecally as part of the preparative regimen.

Health-Related Quality of Life

Patients reported reduced role function, cognitive function, social function and financial difficulties compared to the general population (Table 3). A questionable reduced global quality of life, emotional function and more dyspnea also were found. Diarrhea was the only symptom reported more frequently by the patients. Women reported poorer HRQL than men when compared to gender-specific references. The differences between patients and norms were ten or more in seven scales and items: global quality of life (women only), cognitive function (women), emotional function (women), role and social function (both genders), diarrhea (women), and financial impact (both genders). Fatigue was equally reported by both genders, and did not differ significantly compared with the normal population.

Fatigue and Employment Status

Eighteen patients were employed full-time, whereas 6 and 8 patients, respectively, were part-time employed or not employed at all (employment information missing in 3 patients). Eight of those patients who were partly or not employed were disabled after the disease, and 3 patients were getting through their education. There were clinically and statistically significant differences in fatigue levels between those who were employed full-time (PF 8.3, MF 4.7, TF 12.9), employed part-time (PF 10.7, MF 5.3, TF 16.0), and not employed at all (PF 14.4, MF 6.9 TF 21.3) ($p = 0.01$; 0.05, and 0.02 PF, MF, and TF, respectively). Patients who were disabled reported more fatigue than those who were full- or part-time employed (PF 14.4, MF 7.1, TF 21.5).

Endocrine Status

More than half the women had elevated serum levels of follicle-stimulating hormone (FSH) and leutenizing hormone (LH), while serum levels of estradiol were decreased in 13 of the females (Table 4). Two women were postmenopausal, but were not substituted. Among the men, FSH and LH were elevated in 13 and 6 patients respectively, and low levels of testosterone were found in 6 patients.

Gonadal dysfunction expressed by high levels of FSH (>20 IU/L for women, > 12 IU/L for men) and low levels of estradiol (<0.33 nmol/l; women) and testosterone (<12 nmol/l; men)

Table 3
EORTC QLQ-C30 Mean Scores by Gender and Age

	ABMT (n = 32)	Reference Population (n = 1404)	ABMT Female (n = 15)	Female Reference Population (n = 636)	ABMT Male (n = 17)	Male Reference Population (n = 768)
Global QOL (QOL2)	69[a]	77[a]	63	75	74	79
Functioning scale[d]						
Physical (PF)	92	95	88	93	95	96
Role (RF)	76[b]	87[b]	74	85	76	89
Emotional (EF)	75[a]	82[a]	66	79	83	85
Cognitive (CF)	75[c]	89[c]	69	88	80	89
Social (SF)	68[c]	87[c]	64	85	71	90
Symptom scale[e]						
Fatigue (FA)	34	28	35	32	33	25
Nausea/vomiting (NV)	4	4	7	5	2	3
Pain (PA)	20	18	22	22	19	15
Dyspnea (DY)	19[a]	11[a]	18	15	20	13
Insomnia (SL)	20	18	24	21	16	15
Appetite loss (AP)	14	7	16	9	12	6
Constipation (CO)	10	8	9	12	12	5
Diarrhea (DI)	21[b]	9[b]	29	9	14	9
Financial difficulties (FI)	22[c]	9[c]	27	11	18	7

[a] $p < 0.05$ for differences in mean scores, patients and reference group.
[b] $p < 0.01$ for differences in mean scores, patients and reference group.
[c] $p < 0.001$ for differences in mean scores, patients and reference group.
[d] Higher scores indicates better functioning.
[e] Higher scores indicates more symptoms.

Table 4
Endocrine Status (Serum Levels) after ABMT

	Females (n = 15)	Males (n = 17)
Hb		
< 11.5 g/dl females	1/15	
< 13 g/dl male		5/17
TSH > 4.0 mIE/l)	1/15	
FT4 < 9 pmol/L)	1/15	
FSH		
> 20 IU/L females	9/15	
> 12 IU/L males		13/17
LH		
> 15IU/L females	8/15	
> 12 IU/l male		6/17
Estradiol < 0.33nmol/L	13/15	
Testosterone < 12 nmol/l		6/17

were compared to levels of fatigue to test whether gonadal dysfunction was related to fatigue among ABMT patients. Nine patients had reduced ovarian functioning, and the levels of fatigue did not differ from those with normal hormone levels (5 patients) (PF 12.6, MF 6.6, TF 19.1 vs. PF 11.3, MF 4.8, TF 16.2; n.s.). A similar finding occurred in men with no differences in fatigue levels between patients with impaired (n = 4) versus males with normal gonadal function (n = 14) (PF 8.8, MF 4.8, TF 13.5 vs. PF 8.0, MF 4.6, TF 12.6; n.s.)

Thyroid function was not impaired, and only 1 woman and 5 men had a slightly reduced hemoglobin level. No association between hemoglobin level and fatigue was found.

Serum Levels of IL-6, TNF, and sTNFR

The serum levels of TNF were below 600 pg/ml in 31 of 33 patients. Only two male patients had detectable biological activity of TNF, with serum levels of 870 pg/ml and 963 pg/ml. The clinical status and fatigue levels of those patients did not differ from the rest of the study population. Serum levels of IL-6, sTNFR-p55, and sTNFR-p75 were slightly elevated in all clinical groups of lymphoma patients compared to normal controls (Table 5). A trend was found in the difference of p75 receptors with advanced stage ($p = 0.07$). Treatment burden or time since treatment did not seem to have any influence on levels of the measures.

There were no statistically significant correlation between fatigue (TF) and serum levels of IL-6, TNF, sTNFR-p55, and p75 receptors.

Discussion

The present study demonstrates that fatigue is highly prevalent in this cohort of long-term lymphoma survivors treated with ABMT. The differences in levels of fatigue between the patient population and the reference group are highly significant. Among patients cured for Hodgkin's disease,[17] the level of fatigue was found to be between the present ABMT cohort and the reference population. It has been postulated that fatigue in the HDS survivors may reduce their quality of life significantly[17] and

Table 5
Serum Levels of sTNFRs and IL-6 in Patients Cured of Malignant Lymphoma and Control Groups (Normal Population)

	sTNFR		IL–6
	p55 median (range)	p75 median (range)	median (range)
Controls (n = 10)	1.05 (0.70–1.50)	1.50 (0.90–2.30)	4.80 (3.20–11.0)
Patients (n = 33)	1.39 (0.60–2.20)	1.60 (0.70–2.90)	4.90 (2.70–11.0)
Fatigue level[a]			
high (n = 17)	1.30 (0.60–2.20)	1.60 (0.70–2.90)	4.90 (2.70–10.80)
low (n = 16)	1.30 (0.60–1.90)	1.60 (0.90–2.40)	5.05 (2.90–11.00)
Burkitts lymphoma/lymphoblastic lymphoma	1.15 (0.30–1.90)	1.45 (0.20–2.40)	5.70 (2.70–11.00)
Intermediate grade/Low grade Lymphoma /HD	1.30 (1.10–2.20)	1.70 (1.30–2.90)	4.90 (2.70–10.80)
Stage			
I (n = 6)	0.95 (0.80–1.40)	1.25 (0.90–2.00))	4.50 (3.60–8.30)
II (n = 3)	1.30 (0.70–0.60)	1.60 (0.70–1.90)	5.80 (2.70–6.80)
III (n = 7)	1.30 (1.10–1.80)	1.80 (1.60–2.30)	4.60 (3.20–10.80)
IV (n = 14)	1.25 (0.60–1.90)	1.60 (0.70–2.40)	5.05 (2.70–11.0)
Substage			
A (n = 17)	1.20 (0.60–1.80)	1.60 (0.70–2.30)	5.40 (2.70–10.80)
B (n = 12)	1.30 (0.60–1.90)	1.60 (0.70–2.40)	4.85 (2.70–11.0)

[a] Mean total fatigue score, high: TF 19.6; mean total fatigue score, low: TF 10.5.

also reduce their working ability.[35] Taking these findings into consideration, the high level of fatigue was expected. However, the findings should be interpreted with caution due to the relatively small sample size.

A general tendency was found towards reduced HRQL as compared to the reference populations. Similar findings have been reported in several other studies following patients treated with high-dose therapy.[6,7,36] However, the differences in the HRQL are smaller than for fatigue. This finding may indicate that fatigue is one of the most distressing subjective side effects after ABMT for lymphoma.

The fatigue scale within the EORTC QLQ-C30 did not pick up a significant difference between the ABMT patients and the reference population. This finding might indicate that the 3-item scale within the EORTC QLQ-C30 is not sensitive enough, or it may measure other domains of fatigue than the FQ does. The latter explanation does not seem reasonable because the content of the EORTC QLQ-C30 fatigue scale is very similar to some of the items within the physical fatigue scale.

To investigate possible explanations for persisting fatigue, two major lines were followed, an immunological and an endocrine. Weak relationships were found between serum levels of sTNFR, TNF, and IL-6 on one hand and fatigue on the other. This was not an unexpected finding, since the levels of cytokines were not elevated in our patients. In previous studies, increased levels of cytokines have been found in patients with malignant lymphoma.[37–39]

It has been postulated that cytokines may produce fatigue in humans.[20,21,23] In a study of 70 patients with chronic fatigue syndrome (CFS), immune dysregulation, with particular focus on dysregulation in TNF expression, was proposed as a possible biological marker of fatigue.[40] The findings in the present study were consistent with previous data on immune dysregulation among patients with CFS.[41,42] In another study, elevated serum levels of IL-1 during radiotherapy was found in patients with prostatic cancer at the same time as they reported high level of fatigue.[22] In contrast, Morant[43] did not find any correlations between fatigue on the one hand and TNF, IL-1, IL-2, IL-6, sIL-1, and sIL-2 on the other. A direct comparison between our study and the above mentioned studies might be difficult due to differences in patient cohort, different methods of measuring fatigue, and different methods used to measure cytokines.

Even if no differences were found in levels of cytokines between patients and controls in our study, the hypothesis of long-term effects of cytokines on fatigue should not be rejected. There may be other cytokines of interest, such as IL-1 and IL-2. The effects on the central nervous system, on muscles, and on the endocrine system after long-term exposure of cytokines would be of special interest to investigate in the oncology population.

A gender difference has been shown for fatigue[16] and HRQL[29] in the reference population. In the ABMT cohort, the gender differences were large compared to the findings in the normal population. The gender differences were most pronounced for physical fatigue, which was reported by women to be significantly higher than men. The explanation for this difference is unknown. It might theoretically be related to both biological and/or psychological factors.

A highly significant difference also was observed in the younger female group (15–39 years) compared to women aged 40–60 years. Gonadal dysfunction with elevated FSH and reduced levels of estradiol was found in the majority of the women, but an association with fatigue failed to appear. From a clinical perspective, the high prevalence of ovarian dysfunction is of great importance. Loss of ovarian function occurs in all women immediately after autologous and allogenic bone marrow transplantation and is caused by injuries to the ovaries.[44] In a recent study, recovery of ovarian function was found in one-third of the patients, and was predicted by younger age. Total body irradiation (TBI), however, seemed to have a negative effect on recovery of ovarian function.[24] In our study population, 93% of the women (n = 14) received TBI and cyclophosphamide, one of the most toxic regimens for ovaries. The lack of association between fatigue and the endocrine function in our patients may be due to a combination of the very high prevalence of fatigue and reduced gonadal function, and a very small sample size. It would also have been of interest to measure testosterone among the women. It is likely that testosterone levels are impaired in women with gonadal dysfunction.

Long-term hormone therapy with estradiol and testosterone is reported to have a positive effect on loss of energy in some women.[45] The findings suggest further follow-up studies of cancer survivors, which should measure the development of fatigue and altered gonadal function over time.

Neurotoxicity is an important issue for survivors after high-dose therapy. In several studies, cognitive impairments have been associated with TBI[4,48] as well as with high-dose chemotherapy.[3] Methotrexate is considered to be one of the most neurotoxic drugs. Reduced cognitive functioning among cancer survivors has been reported in several studies[46,47] and may be related to fatigue, especially mental fatigue. In our study, cognitive function, as measured by the EORTC-QLQ-C30, was significantly reduced compared to the general population (Table 3), and correlated significantly with fatigue ($r = 0.52$, $p < 0.01$; data not presented). In a cross-sectional study, it might be difficult to determine whether cognitive impairments are related to the treatment or to pre-existing cognitive problems. However, half of the patients received high-dose methotrexate, and some also received methotrexate intrathecally before the ABMT. Patients who received high-dose methotrexate as a preparative regimen were more fatigued and reported reduced cognitive functioning, as compared to patients who did not receive this type of treatment. Cognitive function items are increasingly included in quality of life measures. The validity of a brief cognitive function scale, like the one included in EORTC-QLQ-C30, is questioned.[46] Studies among cured lymphoma patients have shown that their reports of memory and concentration problems appear to reflect affective disorder and mental fatigue. Using well validated objective neuropsychological tests is recommended for assessing higher mental function.[3,47]

In the absence of information about psychiatric distress, this study is somewhat limited by the uncertainty of the constitution of fatigue. A relation between negative affect and fatigue has been suggested, and depression in particular is considered to be a contributor to fatigue.[35] In a study of Hodgkin's disease survivors, chronic fatigue was associated with increased levels of anxiety and depression.[49] However, no association between previous psychiatric morbidity and fatigue was found. In our study, we found moderate correlation between fatigue and mental distress assessed by EORTC-QLQ-C30 ($r = -0.63$, -0.52, and -0.62, PF, MF, and TF, respectively; $p = 0.01$). The relationship between fatigue and psychiatric distress is far from clear. Both biological correlates and the relation to psychiatric disorders should be explored in further studies of fatigue in cancer patients.

This study has shed light on a prevalent, but poorly understood, phenomena—fatigue—in patients cured of cancer. Fatigue is multidimensional, and the pathophysiology remains uncertain. Significant endocrinological or immunological associations with fatigue could not be demonstrated in the present study. Because high-dose chemotherapy for cancer aims to achieve long-term survival and should allow patients to regain an acceptable life style after completion of treatment, recognition and investigation of fatigue after cancer treatment should be addressed in future research.

Acknowledgments

Financial support for this study was provided by Janssen-Cilag AS. A special thanks to the Norwegian Radium Hospital, Department of Oncology, for allowing us the examination of their patients.

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Paper IV

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Paper V

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Appendices

EORTC QLQ-C30

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette en ring rundt det tallet som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar. Alle opplysningene vil bli behandlet konfidensielt.

	Nei	**Ja**
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	1	2
2. Har du vanskeligheter med å gå en lang tur?	1	2
3. Har du vanskeligheter med å gå en kort tur utendørs?	1	2
4. Er du nødt til å ligge til sengs eller sitte i en stol det meste av dagen?	1	2
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	1	2
6. Er du redusert på noen måte slik at du ikke kan arbeide eller gjøre husarbeid?	1	2
7. Er du helt ute av stand til å arbeide eller gjøre husarbeid?	1	2

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**Endel**	**Svært mye**
8. Har du vært tung i pusten?	1	2	3	4
9. Har du hatt smerter?	1	2	3	4
10. Har du hatt behov for å hvile?	1	2	3	4
11. Har du hatt søvnproblemer?	1	2	3	4
12. Har du følt deg slapp?	1	2	3	4
13. Har du hatt dårlig matlyst?	1	2	3	4
14. Har du vært kvalm?	1	2	3	4
15. Har du kastet opp?	1	2	3	4
16. Har du hatt treg mage?	1	2	3	4
17. Har du hatt løs mage?	1	2	3	4

Bla om til neste side

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**Endel**	**Svært mye**
18. Har du følt deg trett?	1	2	3	4
19. Har smerter påvirket dine daglige aktiviteter?	1	2	3	4
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	1	2	3	4
21. Har du følt deg anspent?	1	2	3	4
22. Har du følt deg engstelig?	1	2	3	4
23. Har du følt deg irritabel?	1	2	3	4
24. Har du følt deg deprimert?	1	2	3	4
25. Har du hatt problemer med å huske ting?	1	2	3	4
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	1	2	3	4
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	1	2	3	4
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	1	2	3	4

Som svar på de neste spørsmålene sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand

29. Hvordan har din fysiske tilstand vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

Dato for utfylling: ☐☐.☐☐.☐☐ Pasient nr. ☐☐☐
Dag Mnd År

Fatigue

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måned. Vennligst besvar alle spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenligner deg med hvordan du følte deg sist du var bra. Sett kun ett kryss for hvert spørsmål.

Har du problemer med at du føler deg sliten?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Trenger du mer hvile?	☐ *Nei, mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Føler du deg søvnig eller døsig?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du problemer med å komme i gang med ting?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Mangler du overskudd?	☐ *Ikke i det hele tatt*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du redusert styrke i musklene dine?	☐ *Ikke i det hele tatt*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Føler du deg svak?	☐ *Mindre enn vanlig*	☐ *Som vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du vansker med å konsentrere deg?	☐ *Mindre enn vanlig*	☐ *Som vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Forsnakker du deg i samtaler?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Er det vanskeligere å finne det rette ordet?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Hvordan er hukommelsen din?	☐ *Bedre enn vanlig*	☐ *Ikke verre enn vanlig*	☐ *Verre enn vanlig*	☐ *Mye verre enn vanlig*

Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (ett kryss)

- Mindre enn en uke ☐
- Mindre enn tre måneder ☐
- Mellom tre og seks måneder ☐
- Seks måneder eller mer ☐

Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (ett kryss)

- 25% av tiden ☐
- 50% av tiden ☐
- 75% av tiden ☐
- Hele tiden ☐

Vennligst kontroller at du har besvart alle spørsmålene

Draft

40040

HADS

Studienr. ☐ Pasientnr. ☐☐☐ Dato(dd.mm.åå) ☐☐☐☐☐☐

Her kommer noen spørsmål om hvordan du har følt deg den siste uken. Sett bare et kryss for hvert spørsmål. Ikke tenk for lenge på svaret - det er din umiddelbare reaksjon på hvert spørsmål som er interessant.

1. Jeg er nervøs eller anspent
   - ☐ For det meste
   - ☐ Ofte
   - ☐ Noen ganger
   - ☐ Ikke i det hele tatt

2. Jeg gleder meg fortsatt over ting jeg pleide å glede meg over
   - ☐ Avgjort like mye
   - ☐ Ikke fullt så mye
   - ☐ Bare lite grann
   - ☐ Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig kommer til å skje
   - ☐ Helt sikkert og svært ille
   - ☐ Ja, men ikke så veldig ille
   - ☐ Litt ille, men det bekymrer meg ikke så mye
   - ☐ Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner
   - ☐ Like mye som jeg alltid har gjort
   - ☐ Ikke like mye nå som før
   - ☐ Avgjort ikke så mye nå som før
   - ☐ Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer
   - ☐ Veldig ofte
   - ☐ Ganske ofte
   - ☐ Av og til
   - ☐ En gang i blant

6. Jeg er i godt humør
   - ☐ Aldri
   - ☐ Noen ganger
   - ☐ Ganske ofte
   - ☐ For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet
   - ☐ Ja, helt klart
   - ☐ Vanligvis
   - ☐ Ikke så ofte
   - ☐ Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere
   - ☐ Nesten hele tiden
   - ☐ Svært ofte
   - ☐ Fra tid til annen
   - ☐ Ikke i det hele tatt

9. Jeg føler meg urolig liksom jeg har sommerfugler i magen
   - ☐ Ikke i det hele tatt
   - ☐ Fra tid til annen
   - ☐ Ganske ofte
   - ☐ Svært ofte

10. Jeg har sluttet å bry meg om hvordan jeg ser ut
    - ☐ Ja, helt klart
    - ☐ Jeg bryr meg ikke så mye som jeg burde
    - ☐ Det kan nok hende jeg ikke bryr meg nok
    - ☐ Jeg bryr meg om utseendet like mye som jeg alltid har gjort

11. Jeg føler meg rastløs som om jeg stadig må være i aktivitet
    - ☐ Uten tvil svært mye
    - ☐ Ganske mye
    - ☐ Ikke så veldig mye
    - ☐ Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting:
    - ☐ Like mye som jeg alltid har gjort
    - ☐ Heller mindre enn jeg pleier
    - ☐ Avgjort mindre enn jeg pleier
    - ☐ Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk
    - ☐ Uten tvil svært ofte
    - ☐ Svært ofte
    - ☐ Ikke så veldig ofte
    - ☐ Ikke i det hele tatt

14. Jeg kan glede meg over en god bok eller et radio eller et TVprogram
    - ☐ Ofte
    - ☐ Fra tid til annen
    - ☐ Ikke så ofte
    - ☐ Svært sjelden

Skjema utarbeidet ved Enhet for anvendt klinisk forskning / Kontor for klinisk kreftforskning
Tlf.: 73 86 72 71/73 86 84 44

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Karnofsky Index

Kriterier for aktivitesstatus ved skjelettmetastatisk kreftsykdom

Utfører normal aktivitet, trenger ikke spesielt stell	100%	Normal. Ingen plager eller subjektive tegn på sykdom.
	90%	Klarer normal aktivitet, sykdommen gir lite symptomer.
	80%	Klarer med nød normal aktivitet. Sykdommen gir en del symptomer.
Ute av stand til å arbeide. Klarer seg hjemme, greier personlig stell. Trenger varierende grad av hjelp.	70%	Klarer seg selv, ute av stand til normal aktivitet aller aktivt arbeid.
	60%	Trenger noe hjelp, men klarer stort sett å tilfredstille egne behov.
	50%	Trenger betydelig hjelp og stadig medisinsk omsorg.
Ute av stand til å greie seg selv. Avhengig av pleie. Sykdommen i progresjon.	40%	Ufør, trenger spesiell hjelp og omsorg.
	30%	Helt ufør, hospitalisering nødvendig, men fare for død er ikke overhengende.
	20%	Svært syk, hospitalisering og understøttende behandling nødvendig.
	10%	Moribund, dødsprosessen er i rask fremmarsj.
	0%	Død

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94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS

251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS

280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
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