# Quality of Life
# in Patients with
# Malignant Blood Disorders

## – a Clinical and Methodological Study

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# ABSTRACT

The overall aim of this thesis was to evaluate and, improve measurements of, health-related quality of life (HRQL) in patients with malignant blood disorders. Patients undergoing autologous stem cell transplantation (SCT), long-term (>5 years) survivors of Hodgkin's lymphoma (HL) and a randomly selected control group were studied. Participants were evaluated with five well-known standardized questionnaires measuring aspects of HRQL and a novel individualized measure, translated and extended for this study: the Schedule for the Evaluation of Individual Quality of Life – Direct Weighting (SEIQoL-DW).

The majority of patients undergoing autologous SCT reported a rather good physical functioning during the first year of follow-up. Most impairment was rated in social function both before and after SCT. Most frequently reported symptoms were fatigue, appetite loss, dyspnoea and many patient described a worsened financial situation. High levels of post-traumatic stress symptoms were recorded, which were related to signs of anxiety and depression.

The long-term survivors of HL, on the other hand, reported few problems related to disease and its treatment and an HRQL in parity with the control group though physical health, as measured with the Short Form 12 (SF-12), was diminished in the patient group. The results of the SEIQoL-DW showed that the areas viewed as most important in life (>50% of patients and controls), were family, personal health, work and relations to other people. Thoughts and worries concerning disease, fatigue and loss of energy and late effects on skin and mucous membrane were the most commonly reported problems following HL. Sixty-six percent of the survivors reported a change in their view of life and of themselves. This initial validation of the extended Swedish version of SEIQoL-DW showed it to be a valuable tool in evaluation of HRQL in HL survivors and controls. The results are interesting in revealing both positive and negative HRQL aspects of the disease and its treatment. Important factors influencing perception of HRQL are disease stage, Sense of Coherence and the financial situation.

*Keywords:* Health-related quality of life, Hodgkin's lymphoma, individual quality of life, malignant blood disorders, SEIQoL-DW

Barnen på bussen
säger bla, bla, bla,
bla, bla, bla,
bla, bla, bla,
runt i hela staden.

Papporna på bussen
säger schhh, schhh, schhh,
schhh, schhh, schhh,
schhh, schhh, schhh,
runt i hela staden

Mammorna på bussen
säger sätt dig ner
sätt dig ner,
sätt dig ner
runt i hela staden.

*Barnvisa*

# ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

## I

L. Wettergren, A. Langius, M. Björkholm, H. Björvell. Physical and psychosocial functioning in patients undergoing autologous bone marrow transplantation – a prospective study. *Bone Marrow Transplantation. 1997; 20, 497-502.*

## II

L. Wettergren, A. Langius, M. Björkholm, H. Björvell. Post-traumatic stress symptoms in patients undergoing autologous stem cell transplantation. *Acta Oncologica 1999; Vol 38, No. 4, 475-480.*

## III

L. Wettergren, U. Axdorph, A. Bowling, M. Björkholm, A. Langius. Individual quality of life in long-term survivors of Hodgkin's lymphoma – a comparative study. *Quality of Life Research 2002, in press.*

## IV

L. Wettergren, M. Björkholm, U. Axdorph & A. Langius-Eklöf. Determinants of health-related quality of life in long-term survivors of Hodgkin's lymphoma. *Manuscript submitted for publication.*

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# CONTENTS

# ABBREVATIONS

| | |
|---|---|
| AP | Appetite loss |
| CF | Cognitive function |
| CO | Constipation |
| DI | Diarrhoea |
| DY | Dyspnoea |
| EF | Emotional function |
| EORTC QLQ-C30 | The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- C30 |
| FA | Fatigue |
| FI | Fianancial impact |
| HAD | Hospital Anxiety and Depression scale |
| HRQL | Health Related Quality of Life |
| HL | Hodgkin's Lymphoma |
| IES | Impact of Event Scale |
| M | Mean |
| MCS | Mental Component Summary |
| NV | Nausea/vomiting |
| PA | Pain |
| PCS | Physical Component Summary |
| PF | Physical function |
| QoL | Quality of Life |
| RF | Role function |
| SD | Standard deviation |
| SEIQoL | The Schedule for the Evaluation of the Individual Quality of Life |
| SEIQoL-DW | The Schedule for the Evaluation of the Individual Quality of Life-Direct Weighting |
| SCT | Stem cell transplantation |
| SF-12 | Short Form Health survey |
| SOC | Sense of Coherence |
| SF | Social function |
| QUALY | Quality-adjusted life years |

# BACKGROUND

## MALIGNANT BLOOD DISORDERS

MALIGNANT DISORDERS, which have their origin in the blood marrow and lymphoid tissues, form a heterogeneous group of diseases. Included in this group are patients with acute and chronic leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma (HL) and multiple myeloma. Clinical symptoms are due to the affected blood cells: common symptoms include tiredness, high susceptibility to infection, fever and bleeding. Malignant disorders of the hematopoietic and lymphatic tissue constituted 8 % of new malignant cases among males and 7 % among females in Sweden in 1999.

Treatment of acute malignant hematological disorders, such as acute leukemia and high-grade lymphomas, usually consists of chemotherapy given in repeated cycles. The purpose of such treatment is to cure the disease. The proportion of patients reaching complete remission is relatively high; many do, however, experience a relapse in their disease and are again treated to reach a complete remission. Treatment of chronic malignant blood disorders depends on the diagnosis and the severity of the disease. The variation in treatment is broad: some patients are not treated until symptoms occur, while others are given chemotherapy, irradiation or monoclonal antibodies, alone or in combination. High-dose treatment followed by stem cell transplantation (SCT) has an established role in treatment of selected patient groups. According to protocols, patients with acute and chronic leukemia, non-Hodgkin's lymphoma, HL and multiple myeloma are in certain status of their disease recommended SCT (Gratwohl et al. 2002).

The patients included in this thesis had the diagnoses HL, non-Hodgkin's lymphoma, acute and chronic leukemia, multiple myeloma and plasmocytoma.

### *Hodgkin's Lymphoma*
In Sweden, approximately 170 HL patients are diagnosed yearly (Socialstyrelsen 2001). The disease usually appears in lymph glands, which often are enlarged and engaged at the time of diagnosis.

In industrialized countries, HL shows a typical bimodal age-incidence curve with the first peak at 25-30 years. After 50 years of age, a continuously increasing incidence is observed (MacMahon 1966). Features suggesting a high standard of living in early childhood and a small family size are associated with development of HL in young and middle-aged adults (Gutensohn and Cole 1980). Although the etiology of HL remains unknown, an infectious agent has been suggested to be involved in the pathogenesis of the disease (Wolf and Diehl 1994, Glaser and Jarrett 1996).

The most common classification of disease stage used today is the updated Ann Arbor classification (Table 1, Lister et al. 1989). HL patients receive a treatment according to the stage of the disease and to the presence or absence of various prognostic factors. The most important prognostic factors predicting inferior outcome in advanced disease are age (>45 years), stage IV, low levels of hemoglobin (<105 g/l) and albumin (<40 g/l) (Hasenclever and Diehl 1998). Generally, previously untreated patients with limited disease (stages I-IIA) are given radiotherapy, usually preceded by a few courses of chemotherapy (Björkholm et al. 1977, Brandt et al. 2001). Patients with advanced disease (stages IIB-IV) are given a combination chemotherapy regimen MOPP/ABVD (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD solely and irradiation in cases with bulky disease (Björkholm et al. 1995). Most HL patients reach a complete remission and more than 70% become long-term (>5 years) survivors (Sieber et al. 1999). High-dose chemotherapy followed by autologous SCT has yielded good results in the treatment of patients that have been resistant to primary treatment and in patients with relapse within a year after chemotherapy (Sweetenham et al. 1999, Craddock 2000). Patients who relapse following radiation therapy alone for limited stage HL are usually satisfactorily treated with combination chemotherapy (Diehl and Josting 2000).

Late medical complications due to treatment are a growing problem with the increased number of surviving HL patients (Swerdlow et al. 2000, van Leeuwen et al. 2000). Treat-

**Table 1.  The Ann Arbor staging classification**

| | |
|---|---|
| Stage I | Involvement of a single lymph node region or lymphoid structure |
| Stage II | Involvement of two or more lymph node regions on the same side of the diaphragm or lymphoid structure |
| Stage III | Involvement of lymph node regions or structures on both sides of the diaphragm |
| Stage IV | Diffuse or spread involvement of one or more extranodal site(s) or tissues with or without lymphoid structure |
| A | No symptoms |
| B | Presence of any of the following symptoms<br>1. Unexplained weight loss of >10% of the body weight in the last 6 months.<br>2. Unexplained fever with temperature above 38°<br>3. Night sweats |
| X | Bulky disease: A peripheral lymph node or region >10 cm or a mediastinal mass>1/3 of the mediastinum at T5-6 level on a chest x-ray |
| CS | Clinical stage |
| PS | Pathological stage (in practice determined by staging laparotomy) |

Adapted after Carbone et al. 1971 and Lister et al. 1989

ment may result in secondary malignancy, which is considered the most serious complication (Hoppe 1997). Other reported complications among the already cured are cardiac toxicity (Eriksson et al. 2000), severe infections (Bookman and Longo 1986), hypothyroidism (Peerboom et al. 1992), pulmonary dysfunction (Allavena et al. 1992, Hassink et al. 1993), infertility (Lacher and Redman 1990, Clark et al. 1995) and late effects on the mucous membrane such as gastritis (Henry-Amar and Joly 1996).

### *Stem cell transplantation*

There are two main types of stem cells sources. In autologous SCT the patient serves as her/ his own donor. The purpose of autologous SCT is to allow for a high-dose chemotherapy regimen and/or irradiation that would otherwise be prohibitive because of toxicity to the patient's bone marrow. In allogeneic SCT the stem cells are obtained from a closely or completely matched individual. This is usually a brother or a sister, but may be an unrelated volunteer donor.

The bone marrow produces three major types of blood cells: erythrocytes, platelets and leukocytes. These blood cells all develop from the "stem cells", which are cells in the bone marrow that are capable of re-producing themselves, as well as to differentiate into all three types of blood cells. The majority of stem cells are located in the bone marrow that exists within the cavity of the bones. The pelvic (hip) bones have a large amount of marrow and are easily accessible. Stem cells are also found circulating in the blood stream or "peripheral" blood after a course of chemotherapy and /or stimulation with growth factors. Therefore, these vital stem cells can be collected (stem cell harvest) from the pelvic bone at the back of the hip, or alternatively, from the peripheral blood (apheresis procedure). Once collected, the stem cells can be frozen and stored.

The previously collected blood or marrow stem cells are returned to the patient's body as an intravenous infusion after receiving preparatory treatment with high-dose chemotherapy and/or irradiation. Until the transplanted stem cells begin to function fully and produce new cells, the patient may experience the complications of a depleted bone marrow: a decrease in leukocytes (infection), a decrease in erythrocytes (anemia) and a decrease in platelets (bleeding). Two to four weeks or longer periods may pass before enough new cells are produced to decrease the incidence of these complications. During this time, the patient will need intensive supportive care.

The aggressive treatment, however, is not only associated with a higher percentage of patients being cured but also with an increased morbidity and mortality (Sullivan et al. 1992, Deeg 1994). The growing population of long-term survivors has led to an increased interest in quality of life (QoL) issues in patients undergoing high-dose chemotherapy followed by SCT.

## THE CONCEPT OF HEALTH-RELATED QUALITY OF LIFE

For the past three decades, considerable research has focused on QoL issues. Today, it is more or less taken for granted that an evaluation of a new treatment should include a measure of QoL. There is broad agreement that the concept is multidimensional and subjective (Cella 1992, O'Boyle 1994, Shumaker and Naughton 1995, Bowling 1997). Many diverse areas are incorporated into the concept, such as physical functioning, including symptoms and side effects, treatment satisfaction, the ability to carry on with one's vocation (role functioning), emotional well being and emotional distress, spirituality, the individual's financial situation, social support, maintenance of leisure activities and family functioning, including intimacy and sexuality. Cella and Tulsky (1992) propose that there are four distinct dimensions: physical, functional, emotional and social well being that can be seen as primary, and most QoL aspects can be grouped into these four dimensions. Five dimensions have been identified by Ware (Ware 1987): physical health, mental health, everyday functioning in social activities and in role activities and general perceptions of well being. The author means that the goal in health care is to maximize the health component of QoL. QoL studies have been criticized for being vague (Gill and Feinstein 1994, Hunt 1997, Leplege and Hunt 1997). The World Health Organization Quality of Life Group (WHOQOL Group) has provided a definition of QoL and mean that an individual's position in life in the context of the culture she/he is living in relation to the person's goals, expectations and concerns constitute the personal QoL. They see it as influenced by physical health, psychological state, level of dependence, personal relationships as well as her or his environment (1995).

Several definitions of QoL used in health care research focus on the gap between the expectations and wishes one has regarding life and the person's perceived experiences (Calman 1984, Patrick et al. 1988, Nordenfelt 1991, Shumaker and Naughton 1995). One definition in line with this perspective and the basis for this thesis is the one stipulated by Cella and Tulsky:

> *Quality of life refers to patients' appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal.* (Cella and Tulsky 1988, p. 70)

QoL research has raised intensive discussions and a demand for a distinction between the terms QoL, health-related quality of life (HRQL), health status and functional status (Nordenfelt 1991, Shumaker and Naughton 1995, Smith et al. 1999). HRQL has been distinguished from the wider QoL concept, where the former focuses only on the QoL influenced by disease and health (Shumaker and Naughton 1995, Bowling 1997, p. 7-8). It should be noted, however, that health status can be seen as just a dimension of HRQL. Specialists in the field of HRQL research have reached a consensus that measurement of HRQL should contain at least the dimensions of emotional, physical, social functioning and global perceptions of health and well being (Berzon and Shumaker 1992).

### *A conceptual model for health-related quality of life*

To increase theoretical clarity several conceptual models describing QoL and HRQL have been developed (Bergner 1985, Wilson and Cleary 1995, Ferrans 1996, Patrick and Chiang 2000). A model can be used for choosing measures when designing studies and for analyzing results when evaluating predictors and determinants for HRQL. Wilson & Cleary's conceptual model to explain HRQL, which is used in this thesis, is presented in Figure 1. The
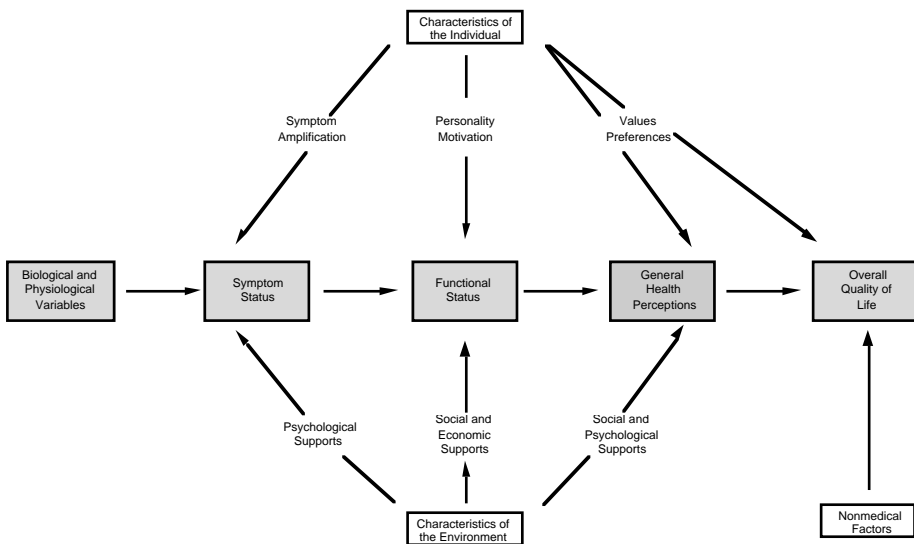


Figure 1. A conceptual model of the relationships among measures of patient outcome in health-related quality of life presented by Wilson & Cleary in JAMA 1995; 273 (1), page 60. Copyrighted (2002), American Medical Association.

authors developed the model with the aim to integrate a biomedical clinical model with a social science paradigm. Measures of patient outcome are categorized and specific causal relationships between different health concepts are proposed.

The model begins with *biological and physiological factors*, including diagnosis, disease stage and time since diagnosis, which affect the perceived symptoms. A *symptom* is the patient's perception of various sensations, such as nausea, fatigue, anxiety and physical restrictions. The next level in the model is *functional status*. Functioning assesses the ability to perform particular tasks (e.g., take a long walk or work full-time). Wilson and Cleary suggest that comprehensive, disease-specific measures of symptoms will be excellent predictors of function (1995). The next level is the perception of *general health*, which has

been shown to be associated with functional status (Barsky et al. 1992). Furthermore, a subjective rating of general health has been shown to have an important influence on *overall QoL* (Michelson et al. 2000). These dominant causal influences are affected by the *characteristics of the individual*, as well as by *environmental characteristics*. Patients' preferences or values play an important role at several points in the model in such a way that certain symptoms are perceived more burdensome than others. Examples of measures of individual characteristics are Sense of Coherence (SOC) (Antonovsky 1987) and Locus of Control (Wallston et al. 1976). Characteristics of the environment are for example the economic and social support the individual receives (de Groot 2002, Michael et al. 2002).

Personality and inner resources are known to have a significant influence on how an individual experiences and judges life (Erikson 1985). Moreover, it is an important factor explaining why patients can perceive the same situation very differently (Weisman 1976, Antonovsky 1987, Massie and Holland 1989, Sprangers and Schwartz 1999). Antonovsky has developed the concept SOC as a resource related to stress (Antonovsky 1987). He includes three dimensions in the concept, comprehensibility, manageability and meaningfulness. It is a particular way of seeing the world, a way that influences the overall capacity to cope with stressful situations. The concept has been operationalized into the SOC scale. High SOC, as measured by the scale, has been shown to be positively related to HRQL(Nilsson et al. 2000, Mendel et al. 2001). SOC is assumed to be a relatively stable trait in adults (Antonovsky 1987). However, traumatic events may change a person's view of life and thus their SOC (Schnyder et al. 2000, Nilsson et al. 2001).

## MEASUREMENT OF HEALTH-RELATED QUALITY OF LIFE

### Who should evaluate?

According to the most commonly used definitions of HRQL, the patient is the most natural person to judge her or his QoL. There are, however, many situations when it is difficult for some patients to judge the situation by themselves. This is particularly the case in patients with dementia, younger children and patients speaking a foreign language. Several studies have shown that a proxy's evaluations of patients' HRQL differ substantially from the patients' self-evaluations in that proxies tend to underestimate physical symptoms and overestimate emotional suffering compared with the patients' self-evaluations (Sprangers and Aaronson 1992, Lampic et al. 1996, Lampic and Sjöden 2000).

Measurements of HRQL can be used for diverse purposes, including to distinguish different patients or groups of patients and to assess patient needs at different periods during and after treatment. Furthermore, in prospective studies HRQL measurements are used to predict patient outcomes and to evaluate therapeutic interventions (Cella 1992, Bowling 1995, Shumaker and Naughton 1995). The results may be helpful in developing nursing and medical care and in planning rehabilitation for patients. It is recommended that measures should capture those elements of HRQL that are sensitive to change over time, can be

reliably and validly assessed and account for most of the variance in an individual's rating of his or her overall well being and HRQL (Bowling 1995, Shumaker and Naughton 1995, Bowling 1997).

### *Standardized questionnaires*

The most common way of measuring HRQL is by using standardized questionnaires, which can be generic, disease-specific or domain-specific. Generic instruments measure aspects that are important to everyone and are useful when different conditions or diseases are compared, whereas disease-specific scales are specifically designed for a particular patient population. A combination of the two types of scales are often preferred in order to be able to compare the results with other groups and to ensure sensitivity to capture specific symptoms and shortcomings (Ware 1993, Bowling 1995). Assessing HRQL with standardized questionnaires makes it possible for the patients to fill the questionnaires out at any place and to take a rest during the task if needed. Nevertheless, it may be burdensome to fill out questionnaires and it is therefore important when studying ill patients to make the battery of measures as small as possible.

A frequently used generic instrument assessing HRQL in cancer patients is the European Organization for Research and Treatment of Cancer Study Group for cancer patients' Quality of Life Core Questionnaire (*EORTC QLQ-C30*) (Aaronson et al. 1993). This generic instrument, which can be easily complemented with site-specific modules, was developed to cover aspects relevant for cancer patients with different diagnoses. It has been translated into several languages and has undergone an impressive level of testing. The results indicate acceptable reliability and validity across different cancer diagnoses and countries (Kaasa et al. 1995, King 1996) including patients with malignant blood disorders (Hjermstad et al. 1999a, Zittoun et al. 1999).

The short-form 36 health survey questionnaire (SF-36) has become the generic measure of choice in the USA and Europe and is frequently recommended as the generic core in disease-specific batteries (Ware and Sherbourne 1992). Short-form 12 is an abbreviated form of the SF-36 developed for use in surveys which may not have room for longer measure with 36 items (Ware et al. 1996). As with the SF-36, the SF-12 has been translated into several languages. In addition, the SF-12 exhibits adequate levels of reliability and validity and is recommended as a practical alternative to the SF-36 (Gandek et al. 1998).

Disease-specific indicators of QoL can be criticized for being too narrowly focused in that they only have items concerning physical symptoms that are caused by the disease and may neglect the measurement of important outcomes and modifying variables (e.g., social support, adjustment, coping, life satisfaction, depression as well as other domains). The domain-specific areas of interest will vary according to how the condition and its treatment affect the patient. An example of a measure frequently used in cancer patients is the Hospital Anxiety and Depression (HAD) scale, which was designed to measure anxiety and depression in physically ill patients (Zigmond and Snaith 1983). The HAD scale is widely used and has been found to have acceptable reliability and validity levels (Moorey et al.

1991, Herrmann 1997) for measuring somatically ill patients, including patients with malignant blood disorders (Razavi et al. 1992, Hjermstad et al. 1999c). The Swedish version (Lundqvist et al. 1991) also appears to be a clinical indicator of depression and anxiety in cancer patients (Larsson et al. 1999b, Nordin et al. 2001).

Another domain-specific instrument that has been increasingly used in cancer patients is the Impact of Event Scale (IES) (Horowitz et al. 1979, Kangas et al. 2002). The IES was developed to measure post-traumatic symptoms of avoidant and intrusive phenomena in two subscales. Intrusion is characterized by unbidden thoughts and/or images of their disease. Conscious denial and avoidance of feelings of and ideas about the disease characterize avoidance. A life threatening illness was quite recently recognized as a stressor that can precipitate posttraumtic stress disorder. The IES has been used in different populations, including cancer patients. Results have thus far indicated that the measure has acceptable reliability and validity levels (Zilberg et al. 1982, Kelly et al. 1995, Nordin and Glimelius 1999).

### *Individualized measures*

Many standardized instruments have been rigorously tested and show good psychometric properties. On the other hand, they are criticized for possibly missing an essential aspect of the patient's perception, primarily because the areas that are evaluated have already been defined (O'Boyle 1994, Bowling 1995). The defenders of individualized instruments reason that if the individual's perspective is to be validly captured, she or he must be permitted to influence each step of the assessment (O'Boyle et al. 1992, Hickey et al. 1996, Waldron et al. 1999). They mean that the issues addressed should be those individuals hold to be important to their QoL and they should then be able to assess the level of functioning or satisfaction in each of these self-nominated areas. Finally, they should indicate the relative personal importance of each area named. Several attempts have been made to capture the individual perception of QoL.

The Patient Generated Index was developed with the aim of having a valid instrument that could quantify the effect of a medical condition on patients' QoL and value improvement in a way that reflects their self-perception of health (Ruta et al. 1994). It is completed in three stages. In the first stage the patients are asked to list the five most important areas or activities of their life that are affected by their condition. In the second stage patients are asked to rate how badly affected they are in each of their chosen areas or activities on a scale. A possibility is also provided to enable them to rate all other areas of their life not previously mentioned. The third and final stage asks patients to imagine that they can improve some or all of the chosen areas/activities of their life.

In cost-utility analyses the cost of an intervention is related to the number of quality-adjusted life years (QUALY). A QUALY is defined as a year of full life quality and poor health may reduce the quality of a year. QUALYs adjust quantity of life by incorporating estimates of preferences or utilities for each health state constituting survival (e.g. a period with post treatment symptoms, recurrence free period, a period with presence of local recurrence)(Torrance 1986).

The influence of satisfaction and importance on the perception of diverse areas constituting HRQL is of great interest and has been evaluated in several studies. Ferrans & Powers developed a QoL index for use in both ill and general populations (Ferrans and Powers 1985). The scores are elicited by means of a set of individual Likert scales and are determined by weighting each satisfaction response with its paired importance response. A Swedish study investigated if HRQL ratings were related to importance-satisfaction discrepancies in the ratings of functioning and symptoms in patients with endocrine tumors (Larsson et al. 1999a, Larsson et al. 1999b). Patients whose ratings of importance were higher than their ratings of satisfaction on the same aspect reported a worse HRQL than did the group with equal or higher satisfaction ratings. Larsson et al. interprets the findings as support for the notion that importance-satisfaction discrepancies are valid indicators of patient distress.

The Schedule for the Evaluation of the Individual Quality of Life (SEIQoL) is an instrument that allows the respondent to choose the most important areas in life crucial to QoL (O'Boyle et al. 1992, O'Boyle 1994). The respondents are asked to rate the five most important domains of satisfaction and importance and then the scores are aggregated to produce an overall score. Judgment analysis is used for this last stage, which allows the various factors that contribute to an overall judgment to be quantified. An abbreviated form, SEIQoL-Direct Weighting (SEIQoL-DW), has been developed and has replaced the judgment analysis technique with a colored disc for the weighting procedure (Hickey et al. 1996, Browne et al. 1997). The SEIQoL-DW have been used in cancer patients including malignant blood disorders (Waldron et al. 1999, Montgomery et al. 2002).

## HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH MALIGNANT BLOOD DISORDERS

### *Patients following stem cell transplantation*

Studies of HRQL in patients with malignant blood diseases undergoing SCT report that patients in the immediate post-transplant period may perceive severe symptoms related to high-dose chemotherapy and total body irradiation. The acute symptoms include nausea and vomiting, loss of appetite, oral mucositis, diarrhea, infections with fever, fatigue and loss of strength, pain and psychological distress (Collins et al. 1989, Chao et al. 1992, Gaston-Johansson et al. 1992, Larson et al. 1993, Meyers et al. 1994, Hjermstad et al. 1999c, Schulz-Kindermann et al. 2002, Larsen et al. in press, Eur J Cancer Care).

The first year after high-dose treatment followed by SCT is reported as physically and mentally stressful. Physical problems include fatigue, eating troubles and physical restrictions; psychological problems include fears about the future, anxiety and depression (Chao et al. 1992, Syrjala et al. 1993, Jenkins et al. 1994, Baker et al. 1999, Hjermstad et al. 1999c).

Financial problems and difficulties in social life are frequently reported, as are problems associated with returning to former roles (McQuellon et al. 1998, Baker et al. 1999, Hjermstad et al. 1999a). Sexual dysfunction and infertility as a result of treatment are additional prob-

lems facing many patients (Marks et al. 1996, McQuellon et al. 1998, Baker et al. 1999, Hjermstad et al. 1999a). After one year, a majority of the surviving patients seem to have recovered quite well from a physical point of view (McQuellon et al. 1998, Baker et al. 1999, Hjermstad et al. 1999b). However, a sizable proportion of patients continue to be troubled with health-related problems (Syrjala et al. 1993, Andrykowski et al. 1995, McQuellon et al. 1998).

In cross-sectional or retrospective studies on late complications infertility and psycho-sexual dysfunction, fatigue, vocational problems and social adjustment have been problems of greatest concern (Wolcott et al. 1986, Bush et al. 1995, Molassiotis et al. 1995, Prieto et al. 1996, Sutherland et al. 1997).

The findings on the occurrence of emotional distress in survivors of SCT vary, with reports of patients suffering from anxiety and depression ranging from 8 to 48% (Lesko et al. 1992, Syrjala et al. 1993, Meyers et al. 1994, Leigh et al. 1995, Hjermstad et al. 1999c). The variation is related to such factors as study design, measures and the time of assessment. Several papers have reported that psychological status before BMT is predictive in determination of long-term adjustment (Zabora et al. 1993, Meyers et al. 1994, Leigh et al. 1995, Hjermstad et al. 1999c).

Many studies comparing patients undergoing allogeneic versus autologous SCT report no differences between the groups in their perception of HRQL after SCT (Molassiotis et al. 1995, Prieto et al. 1996, Hjermstad et al. 1999b). The findings, however, are not consistent with some studies reporting more problems in allogenic patients (Andrykowski et al. 1995, Zittoun et al. 1997) and some reporting the opposite (Sutherland et al. 1997).

The few studies performed on coping behavior in cancer patients following SCT have focused on the use of specific behavioral strategies as adaptive or maladaptive (Syrjala et al. 1993, Jenkins et al. 1994, Litwins and Rodrigue 1994). The results of these studies showed that patients using active coping styles were significantly less anxious and depressed than patients using passive coping styles.

### *Survivors of Hodgkin's Lymphoma*
In survivors of HL the most commonly reported problems concern physical functioning (van Tulder et al. 1994, Joly et al. 1996, Loge et al. 1999b), work (Fobair et al. 1986, Bloom et al. 1993, van Tulder et al. 1994, Abrahamsen et al. 1998), sexuality (Fobair et al. 1986, Bloom et al. 1993, van Tulder et al. 1994, Abrahamsen et al. 1998, Kornblith et al. 1998), infertility (Fobair et al. 1986, Bloom et al. 1993, Abrahamsen et al. 1998), fatigue and lacking in energy (Fobair et al. 1986, Bloom et al. 1993, Joly et al. 1996, Abrahamsen et al. 1998, Loge et al. 1999a) and cognitive function (Bloom et al. 1993, Joly et al. 1996). Financial difficulties because of reduced ability to borrow from banks and because of problems obtaining life and health insurance policies have been reported in studies from Europe and the USA (Kornblith et al. 1992, Bloom et al. 1993, Joly et al. 1996). Concerning psychological sequels, no differences have been found between HL survivors and randomly selected control groups (Fobair et al. 1986, Joly et al. 1996, Loge et al. 1999b).

The reported associations between disease and treatment characteristics and HRQL in survivors are inconsistent in the literature. For instance, some studies have reported com-

bined modality regimens to be associated with reduced QoL (Greil et al. 1999) and an increased risk of emotional distress (Loge et al. 1997) in comparison with either irradiation or chemotherapy alone, but not consistently (Loge et al. 1999b). Time since treatment has been reported to influence HRQL in patients, where the more recently treated are more likely to experience persisting symptoms of nausea and vomiting (Cameron et al. 2001), as well as elevated levels of emotional distress (Cella and Tross 1986, Fobair et al. 1986).

# AIMS OF THE STUDY

THE MAIN PURPOSE of the present study was to characterize and improve measurements of HRQL in patients with malignant blood disorders with the ultimate goal to develop care and rehabilitation in these patient categories. This was approached with the following specific aims:

To evaluate HRQL in patients undergoing autologous SCT

To evaluate HRQL in long-term survivors of HL by comparing the findings with a randomly selected sample drawn from the general population in Stockholm County

To evaluate the extended Swedish version of the SEIQoL-DW in HL survivors and the randomly selected control group

To identify relationships among measures of HRQL by using Wilson & Cleary's conceptual model

# METHODS

Tʜɪs ᴛʜᴇsɪs ᴄᴏɴsɪsᴛs of four clinical studies in patients with malignant blood disorders. Two of the four studies concern patients undergoing autologous SCT and the other two studies pertain to patients who are long-term survivors of HL. A prospective design was used to study the patients undergoing SCT. In these studies three assessments were done over a one-year period. A cross-sectional design was used to study the HL survivors. Papers III -IV also had a methodological implication in testing an instrument that was translated to Swedish and modified for this thesis. The study designs of the four studies described above are descriptive, correlational and comparative.

## SAMPLES

Papers I-IV are based on three samples. Individuals were excluded if they could not speak and read Swedish.

*Papers I and II.* Consecutive patients with malignant blood disorders undergoing autologous SCT at the Division of Hematology at the Karolinska Hospital in Stockholm from 1992 to 1993 were included in the study. The patients participated on three separate occasions: the week before start of high-dose treatment, 4-6 months after SCT (the first follow-up) and 10-12 months after SCT (the second follow-up). All patients received high-dose chemotherapy, 14 in combination with total body irradiation. Patients were excluded from the study if their nurse or physician judged their mental, physical or emotional condition to be too poor to participate. Twenty patients met the eligibility criteria and hence were included in the study. The attrition rate is presented in Figure 2.

*Papers III and IV.* All adult patients with HL treated in Stockholm County during the period 1972 to 1991 and living in Stockholm County in January 1997 were included in the study. The final sample consisted of 196 patients meeting the eligibility criteria. Seventy-five patients were nonresponders, why 121 completed the study (response rate 62%). There were no significant differences between responders and nonresponders regarding demographic and disease characteristics. Clinical characteristics of the responders are summarized in Table 2.

*Papers III and IV.* A random sample of 700 Swedish citizens was selected from the Stockholm County Council's database (Medical Enator) to serve as a control group. The goal was to have a control group of 350 persons, and as the expectation was a response rate

**Figure 2. The samples of patients with malignant blood disorders in paper I and II**
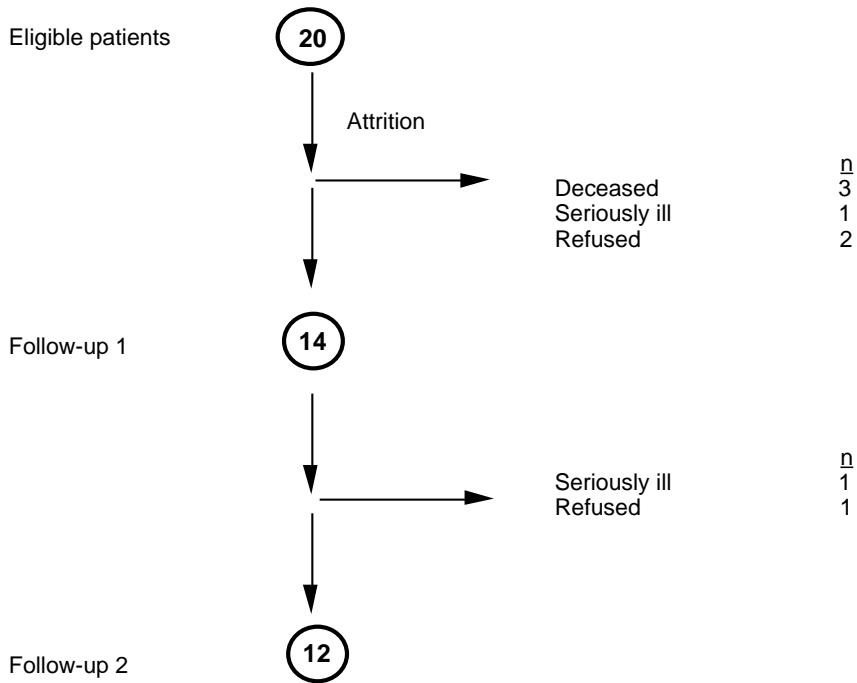
Eligible patients     ( **20** )

           Attrition

|  |  | n |
|---|---|---|
| Deceased |  | 3 |
| Seriously ill |  | 1 |
| Refused |  | 2 |

Follow-up 1     ( **14** )

|  |  | n |
|---|---|---|
| Seriously ill |  | 1 |
| Refused |  | 1 |

Follow-up 2     ( **12** )

**Table 2. Clinical characteristics of longterm survivors of HL, n=121 (Paper III, IV)**

|  | n | % |
|---|---|---|
| Clinical stage |  |  |
| I | 27 | (23) |
| II | 52 | (43) |
| III | 21 | (17) |
| IV | 21 | (17) |
|  |  |  |
| B-symptoms |  |  |
| No | 85 | (70) |
| Yes | 36 | (30) |
|  |  |  |
| Primary treatment |  |  |
| Irradiation | 66 | (55) |
| Chemotherapy | 34 | (28) |
| Irradiation + chemotherapy | 20 | (17) |
| Other | 1 |  |

of only 50%, were 700 persons initially allocated. The low response rate was regarded as probable because of using the interview method of data collection. The controls were stratified according to age and sex: 300 were aged between 25-40 years, 200 between 41-55 years and 200 between 56-70 years, with an equal distribution of women and men in each age group. Nine (<1%) of the selected addresses were ineligible. Totally, 455 participants declined to be interviewed, leaving a final sample of 236 to take part in the study (response rate 34%).

Table 3 presents participant characteristics in Papers I-IV.

**Table 3. Subject characteristics**

|  | SCT patients (n=20) Paper I, II | | HL survivors (n=121) Paper III, IV | | Control group (n=236) Paper III, IV |
|---|---|---|---|---|---|
| Gender, % | | | | | |
| Female | 40 | | 45 | | 56 |
| Male | 60 | | 55 | | 44 |
| Mean age (years) | 37 | | 47 | | 46 |
| (range) | (17-54) | | (23-75) | | (24-70) |
| Diagnosis, n | | | | | |
| Hodgkin's lymphoma | 1 | | 121 | | na |
| Non-Hodgkins lymphoma | 5 | | | | |
| Acute myeloblastic leukemia | 5 | | | | |
| Acute lymphoblastic leukemia | 4 | | | | |
| Chronic myeloblastic leukemia | 3 | | | | |
| Myeloma | 1 | | | | |
| Plasmocytoma | 1 | | | | |
| Disease status at time for interview, n (%) | | | | | |
| First complete remission | 9 | (45) | 89 | (73) | |
| Second complete remission | 5 | (25) | 24 | (20) | |
| Third complete remission | 0 | | 8 | (7) | |
| Partial remission | 2 | (10) | 0 | | |
| Chronic phase | 3 | (15) | 0 | | |
| Progressive disease | 1 | (5) | 0 | | |

na, not applicable

## INSTRUMENTS

An overview of the instruments included in Papers I-IV is given in Table 4.

*EORTC QLQ-C30* (version 1.0) consists of 30 items with five functional scales: physical functioning (PF), role functioning (RF), cognitive functioning (CF), emotional functioning (EF) and social functioning (SF); three symptom scales: fatigue (FA), nausea and vomiting (NV) and pain (PA); and a global health/QoL scale (Aaronson et al. 1993). Single items measure the individual's appetite loss, sleeplessness, dyspnoea, constipation, diarrhea and perceived financial affect as a result of disease and treatment.

As recommended by the EORTC study group, all the scales and item scores in QLQ-C30 were linearly transformed to a 0 to 100 range, with higher scores on the functional scales and the global health/QoL scale representing better functioning and health (Aaronson et al. 1993). For the symptom scale and single items higher scores represent more symptoms.

*The HAD scale* consists of 14 items that have four response choices ranging from 0 (no sign of distress) to 3 (maximum level of distress) (Zigmond and Snaith 1983). It includes two subscales: an anxiety subscale (seven items) and a depression subscale (seven items). The total score of each subscale, derived by summing the score for each item, indicates the extent of anxiety and depression, with higher scores representing greater distress.

The constructors of the scale recommend two cut-off scores: a score of 8-10 points identifies a potential clinical "case" of anxiety and depression and a score of 11 or more indicates a definite clinical "case" (Zigmond and Snaith 1983). In this thesis the lower cut-off level chosen was ≥8 points.

*The SOC scale*. In this study a short form (13 items) of Antonovsky's 29-item scale was used (Antonovsky 1987). Respondents are requested to mark their response for each item on a seven-point scale (e.g., with one indicating never and seven indicating very often). The score from each item is summed up to a total score ranging from 13 to 91 points, with higher scores indicating higher SOC. The English version of the SOC scale has been translated into Swedish (Langius et al. 1992) and both the English and the Swedish version have shown adequate levels of reliability and validity (Antonovsky 1987, Nilsson et al. 2000, Schnyder et al. 2000, Mendel et al. 2001).

**Table 4. Overview of the instruments used in Papers I-IV**

|  | Paper I | Paper II | Paper III | Paper IV |
|---|---|---|---|---|
| EORTC QLQ-C30 | X | X | | |
| HAD | X | X | | X |
| SOC | X | X | | X |
| IES | | X | | |
| SF-12 | | | | X |
| SEIQoL-DW | | | X | X |
| Demographic data sheet | | | X | X |

*IES* measures symptoms of avoidant (eight items) and intrusive (seven items) phenomena (Horowitz et al. 1979). The respondents are asked to report frequency of post-traumatic stress symptoms during the previous week on a four-point scale ranging from not at all (0) to often (5). The respondents included in this thesis were asked to rate their responses with their malignant blood disease in mind. The version used in this thesis (Paper II) was translated into Swedish by two of the authors (HB and LW). A translation was also made by an English native speaker to compare the translations. The total score in the intrusive subscale ranges from 0 to 35 and in the avoidance subscale from 0 to 40 points. Higher scores indicate a greater level of avoidance or intrusion. The authors have suggested three cut-off scores. Scores below 9 points are defined as a minor reaction, between 9 and 19 as a moderate reaction that may warrant further evaluation and scores of 20 or more are suggested to indicate a stress response that merits concern (Horowitz 1982).

*SEIQoL-DW* is an interview-based instrument derived from the full Schedule for the Evaluation of the Individual Quality of Life (SEIQoL) (Hickey et al. 1996, Browne et al. 1997). As in the original version of the SEIQoL-DW, the respondents were first asked the following question: "If you think about your life as a whole, what are the most important things - both good and bad - in your life at present that are crucial for your QoL?" The respondents were free to mention as many domains as they wished. The interviewer wrote down the respondents' statements. In the second stage the respondents were asked to rate their current status (level) for each of the nominated domains on a seven-point category scale. The third stage determined the importance of each domain by direct weighting. The direct weighting instrument is a simple apparatus consisting of five interlocking, colored laminated circular disks that can be rotated around a central point to form a pie-like chart. The proportion of the chart that each sector represents can be scored from 0-100 points on the chart's circumference. Each segment is labeled with one of the life domains nominated by the respondent as being important to his or her overall QoL. The respondent adjusts the disk until the size of each colored segment corresponds to the relative importance of the life domains represented. The rating and the weight for each domain are multiplied and the products aggregated to produce an overall QoL index score, which can range from 1-7.

The instrument was translated into Swedish for this study and the Swedish version was extended with a disease-specific section based on Bowling's work (Bowling 1995).

The HL survivors were additionally asked the following question: "If you think about the fact that you have been treated for HL, what in your life is influenced, both positively and negatively, by this?" The respondents could mention as many domains as they desired. Each domain was then rated on how troublesome or satisfying it was as well as its significance to them. From these ratings, an overall disease index score was calculated. The disease-specific component of the scale was also included in the interviews of the control group. Specifically, the controls were asked if they had any types of physical handicap or longstanding illness.

The original SEIQoL, which has shown satisfactory psychometric properties, estimates reliability and validity through judgment analysis (O'Boyle et al. 1992, O'Boyle 1994, Waldron et al. 1999). The SEIQoL-DW has yielded results comparable to the original SEIQoL

regarding stability and validity, even though the measures are not considered interchangeable (Browne et al. 1997, Waldron et al. 1999, Neudert et al. 2001, Prince and Gerber 2001).

*SF-12* provides two summary outcomes on physical health and mental health: physical component summary (PCS-12) and mental component summary (MCS-12) (Ware et al. 1996). The PCS summarizes physical functioning, role limitations because of physical problems, bodily pain and general health. The MCS summarizes vitality, social functioning, role limitations because of emotional problems and mental health. After coding the raw scores, the items were recalibrated following standard recommendations (Sullivan et al. 1997). The total score in the PCS-12 ranges from 10.55 to 70.13 points and the corresponding figures for MCS-12 are 5.89 to 72.25. A higher score reflects better self-rated health.

*Demographic data* were collected with the help of a questionnaire with seven items developed for Studies III and IV. The items addressed the following variables: sex, age, marital status, having children, education, employment status and the respondents' self-perception of their socioeconomic status.

*Clinical data* was collected from the patients' medical records, including diagnosis, date of diagnosis, stage of the disease, treatment and current disease status.


## PROCEDURES

The Ethics Committee of the Karolinska Hospital approved all studies. All participants were given oral and written information about the study. Informed consent was obtained from all respondents.

*Papers I and II.* Before admission to the hospital for high-dose chemotherapy the patients received written information about the study. A few days after the letter was mailed to the patient, one of he authors (LW) called the patient and asked if she or he was willing to participate. When a patient had agreed to participate, he or she was given a verbal explanation about the study. At follow-up, the questionnaires and an explanatory letter were sent to the patients together with a stamped return envelope. Because SOC is seen as a rather stable trait in adulthood, the scale was completed only once before SCT. At the first follow-up, a study-specific questionnaire was included that focused on the patients' experience and satisfaction with their care during hospitalization. The study-specific questionnaire is not presented as part of this thesis, however.

*Papers III and IV.* All participants received a letter that informed them about the study. The respondents were promised a movie ticket if they participated in the study. A few days after the letter was mailed to the respondent, one of the interviewers called to book a time for an interview for those showing willingness to participate. All interviews took place at the Karolinska Hospital during 1997. Respondents who could not be reached by telephone were sent a reminder by mail.

## DATA ANALYSIS

The statistical methods used in Papers I-IV are presented in Table 5.

### Papers I and II
Chi-square statistics were performed to determine differences in categorical variables. Because most of the scales in the EORTC QLQ-C30 were not normally distributed, non-parametric statistical methods were used for evaluation of the subscales. Differences in median scores of the EORTC QLQ-C30 between baseline, the first follow-up and the second follow-up were studied by Friedman's two-way analysis of variance. A repeated measures ANOVA was conducted for the corresponding evaluation of HAD, SOC and intrusion/avoidance. The Mann-Whitney *U* test was used to investigate whether subgroups differed in their

**Table 5. Overview of the statistical methods used in Papers I-IV and thesis**

|  | Paper I | Paper II | Paper III | Paper IV | Thesis framework |
|---|---|---|---|---|---|
| Chi-square statistics | X | X | X | X | |
| Mann-Whitney *U* test | X | X | | | |
| Paired *t*-test | X | X | | | |
| Unpaired *t*-test | | | X | X | |
| Friedman's two-way analysis of variance | X | X | | | |
| ANOVA repeated measures | X | X | | | |
| ANOVA one-way analysis | | | X | | |
| Spearman rank-order correlation coefficient | X | X | X | | |
| Pearson's product-moment correlation coefficient | X | X | X | | X |
| Multiple regression analysis | | | X | | X |
| Partial correlation coefficients | | | | X | |
| Effect size | | | | X | |
| test of difference between partial correlation coefficients | | | | X | |
| Chronbach's alpha coefficient | X | X | | X | |

ratings on the EORTC QLQ-C30 based on (a) anxiety/depression ratings, (b) nonresponders vs. those who responded to all three assessments and (c) gender. Unpaired t-tests were performed to determine differences in mean scores on the IES and SOC between responders and nonresponders and between women and men. Spearman rank-order correlation coefficients were employed to describe the strength and direction of the relationships between ratings of function and symptoms in the EORTC QLQ-C30 and (a) anxiety/depression, (b) SOC, (c) intrusion/avoidance and (d) age. Pearson's product-moment correlation coefficients were computed to evaluate the relations between anxiety/depression, SOC, intrusion/avoidance and age.

Cronbach's alpha coefficient was used to assess the internal consistency in the SOC, HAD, EORTC QLQ-C30 and IES scales. Coefficients >0.70 are suggested for group-level comparisons to reflect good internal consistency of an instrument (Streiner and Norman 1995). Cronbach's alpha coefficients for the HAD anxiety subscale before SCT and at the first and second follow-ups were 0.87, 0.90 and 0.88, respectively. The corresponding figures for the depression subscale were 0.62, 0.67 and 0.86, respectively. For most of the subscales in the EORTC QLQ-C30, the alpha coefficients were above 0.70. Not one of the coefficients was below 0.45. Cronbach's alpha coefficient for the SOC scales was 0.79. The alpha coefficients for the IES intrusion subscale before SCT and at the first and second follow-ups were 0.90, 0.73 and 0.60, respectively. The corresponding figures for the avoidance subscale were 0.73, 0.80 and 0.86, respectively.

## Papers III and IV

To test differences in categorical data chi-square statistics was performed. Unpaired *t*-tests were used for comparisons between the patients and controls on (a) the satisfaction ratings of the areas of importance in the SEIQoL-DW and (b) the mean scores on the QoL global index, PCS and MCS of SF-12 and the anxiety and depression subscales of the HAD. The effect size was calculated to indicate the clinical meaningfulness of the significant difference that was found in the mean scores between the groups (Fayers and Machin 2000). The mean difference between the groups was divided by the standard deviation (SD) in the control group. It is suggested that an effect size of 0.20 to 0.50 be regarded as "small", 0.50 to 0.80 as "moderate" and those 0.80 or above as "large." One-way ANOVA was performed to test for differences between the three interviewers in the ratings and in the QoL index of the SEIQoL-DW. Spearman's rank correlation coefficient was used to evaluate the relation between the number of areas that was influenced by disease and the time since diagnosis. Correlations between variables were tested using Pearson's product moment correlation coefficients. Multiple regression analyses were performed within the HL sample and within the control group. The independent variables in the HL survivors included age, sex, time since diagnosis, disease stage (I-IV), irradiation vs. no irradiation, chemotherapy vs. no chemotherapy and combined modality vs. single modality. The dependent variables were the QoL index and the disease index of the SEIQoL-DW. In the control group the independent variables were age and sex and the dependent variable was the QoL index of the SEIQoL-DW. Partial correlations, controlling for age and sex, were used for analysis of the relations between the variables included in the model. The partial correlation coefficients were trans-

formed from r to z scores to test if an observed correlation among the HL survivors differed from the control groups' corresponding figures (Snedecor and Cochran 1980, p. 186-187).

Cronbach's alpha coefficient for the HAD anxiety subscale in the HL survivors was 0.84 and in the general population 0.77. The corresponding figures for the depression subscale were 0.68 and 0.62, respectively. Coefficients for the SOC scale were 0.82 in the HL survivors and 0.79 in the general population.

P-values <0.05 were considered statistically significant.

### Framework of the thesis

Comparisons of patient ratings on the EORTC QLQ-C30 and Swedish normative data were made after making adjustments for age and gender (Michelson et al. 2000) (Paper 1). The expected mean scores were selected using the Swedish population reference score for each age and gender group (Hjermstad et al. 1998). A difference of >10 points between an observed and expected value was considered as a meaningful change (King 1996).

To further investigate the outcome measures of the extended SEIQoL-DW multiple regression analyses were performed with the QoL global index in each sample separately and when the two samples are merged. The independent variables used in these analyses were PCS, MCS, SOC, age and gender. For the HL survivors, in addition to the above independent variables, disease index, time since diagnosis and disease stage were included in the analyses.

To evaluate the influence of the weighting procedure the correlations between the standardized questionnaires and the QoL global index with weighting were compared with the sum of the ratings without weighting (Paper IV). Furthermore, a multiple regression analysis was computed with the QoL global index as the dependent variable and the sum of the ratings as the independent variable.

### Analysis of the answers to the open-ended questions of the SEIQoL-DW

The respondents' answers to the questions in the extended SEIQoL-DW were written down directly during the interview. The patients' answers were transcribed and the transcript was divided into units to allow for coding. A unit was defined as a single word or a brief sentence that represented a content of QoL. One of the authors (LW) carried out the analysis of the transcripts. The list of domains published by Bowling was used as an initial framework for the categorization process (Bowling 1995). The categories were not mutually exclusive and thus a unit could be defined in more than one category when this was deemed suitable. Another author (AL) read these categorizations. Approximately 80% of these categorizations were in accordance with the first author's classification. The process of categorization involved repeated meetings with discussions and comparison within data. In this process domains were either modified or added until agreement was reached among the two authors.

### Internal attrition

When a HAD or SOC questionnaire was partially incomplete, the scale values were estimated by assuming that the missing item had a value equal to the average of those items that

were present, provided that no more than two items of the scale were missing. For the EORTC QLQ-C30 and SF-12 scales, if an item was missing, that entire subscale was excluded.

StatView 5.0, 1992-98 SAS Institute Inc. for Macintosh was used for statistical analyses, except for the partial correlations and the test of coefficient difference, which were performed with SPSS Base 11.0 system for Windows. QRS NUD•IST revision 4 for Apple Macintosh was used when categorizing the answers to the open-ended questions of the SEIQoL-DW.

# RESULTS

## PAPER I

THERE WERE NO significant changes in the functional or symptom scales of the EORTC QLQ-C30 before and during the first year after SCT. The lowest functional scores were given to SF (median 67) at all three assessments, as well as in RF (median 50) and global health/QoL (median 67) at the first follow-up. The symptoms of dyspnoea (median 33 points), sleep disturbances (median 33 points) and fatigue (median 22 points) were rated most frequently before SCT. At the first and second follow-ups, fatigue (median 39 and 28, respectively) and dyspnoea (median 33 points at both follow-ups) were still the most often rated symptoms. The financial impact of the disease and the treatment was 33 points before SCT and at the first follow-up, but declined to 0 points at the second follow-up.

Patient ratings of EORTC QLQ-C30 differed from the expected scores of a reference group consisting of the Swedish population (Michelson et al. 2000) of similar age and gender before SCT and at both follow-ups (Table 6). The results indicate that the patients included in Papers I and II perceive their HRQL as worse compared with adults, with the greatest impairments recorded at the time of the first follow-up. This period is the stage when patients are expected to still be recovering after treatment.

Levels of anxiety and depression were relatively high before SCT and did not significantly change during the first year. At the time the study was performed, there were no Swedish reference values published for the HAD scale. Therefore, the mean values from the present study were compared with those from the control groups (i.e. the control groups who participated in Papers III and IV)

The mean value of anxiety before SCT and the mean depression value on all three assessments (i.e., before SCT, and at the two follow-up sessions) were higher in patients compared with controls, though these differences reached statistical significance on only two assessments. Approximately one third of the patients (n=7) before SCT, five patients at the first follow-up and four patients at the second follow-up reached levels indicating a clinical "case" of anxiety. The corresponding number of "cases" regarding depression was six before SCT and two at each of the follow-ups.

Significant differences were found between anxiety "cases" and "non-cases" for three EORTC QLQ-C30 scales: EF at all three assessments and CF and Global health/QoL at the second follow-up.

The mean score from the SOC scale was 67.0 (SD 11.9). Some significant relationships were found between the SOC scale and the functional scales of EORTC QLQ-C30: RF (r=0.46, p≤0.05), SF (r=0.62, p≤0.01) and Global health/QoL (r= 0.67, p≤0.01) before SCT; and PF (r= 0.68, p≤0.05) and SF (r= 0.64, p≤0.05) at the second follow-up. These findings

**Table 6. Expected (population based) and observed scores for the EORTC QLQ-C30 scales and single items in patients undergoing SCT (papers I and II)**

| | Prior SCT, n=19 | | | Follow-up 1, n=14 | | | Follow-up 2, n=12 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Observed scores M | Expected scores M | Obs-Exp Diff | Observed scores M | Expected scores M | Obs-Exp Diff | Observed scores M | Expected scores M | Obs-Exp Diff |
| Physical functioning[a] | 92.6 | 93.9 | -1.3 | 80.0 | 93.7 | **-13.7** | 85.0 | 93.5 | -8.5 |
| Role functioning[a] | 60.5 | 87.9 | **-27.4** | 60.7 | 87.8 | **-27.1** | 79.2 | 87.7 | -8.5 |
| Cognitive functioning[a] | 82.4 | 88.9 | -6.5 | 83.3 | 88.7 | -5.4 | 72.1 | 88.6 | **-16.5** |
| Emotional functioning[a] | 62.6 | 78.0 | **-15.4** | 74.3 | 77.0 | -2.7 | 75.0 | 77.1 | -2.1 |
| Social functioning[a] | 59.7 | 90.4 | **-30.7** | 60.7 | 90.1 | **-29.4** | 64.0 | 89.9 | **-25.9** |
| Global quality of life[a] | 70.1 | 76.7 | -6.6 | 60.1 | 76.0 | **-15.9** | 70.1 | 76.4 | -6.3 |
| Fatigue[b] | 26.2 | 21.3 | +4.9 | 42.7 | 21.8 | **+20.9** | 30.5 | 21.7 | +8.8 |
| Nausea and vomiting[b] | 2.7 | 3.7 | -1.0 | 19.1 | 3.8 | **+15.3** | 9.8 | 3.6 | +6.2 |
| Pain[b] | 15.8 | 17.2 | -1.4 | 11.8 | 17.5 | -5.7 | 26.2 | 17.7 | +8.5 |
| Dyspnoea[b] | 26.3 | 16.7 | +9.6 | 42.8 | 15.7 | **+27.1** | 30.5 | 15.1 | **+15.4** |
| Sleep disturbance[b] | 26.2 | 16.1 | **+10.1** | 14.2 | 16.6 | -2.4 | 25.1 | 16.8 | +8.3 |
| Appetite loss[b] | 15.7 | 4.7 | **+11.0** | 26.1 | 4.5 | **+21.6** | 8.2 | 4.1 | +4.1 |
| Constipation[b] | 1.7 | 4.6 | -2.9 | 2.3 | 5.2 | -2.9 | 2.8 | 5.5 | -2.7 |
| Diarrhoea[b] | 3.5 | 5.9 | -2.4 | 7.1 | 6.0 | +1.1 | 8.3 | 6.0 | +2.3 |
| Financial impact[b] | 38.5 | 6.4 | **+32.1** | 23.6 | 6.4 | **+17.2** | 25.0 | 6.4 | **+18.6** |

[a] Scores range from 0 to 100. A higher score represents a higher level of functiong.
[b] scores range from 0 to 100, a higher score represents a higher level of symptoms.
Differences >10 points between observed and expected scores are in bold and indicate that the difference may be clinically important.

indicate that the more diminished the function, the lower the SOC score. Only on two occasions were the symptom scales of EORTC QLQ-C30 significantly associated with SOC: fatigue (r=-0.49, p<0.05) and appetite loss (r=-0.57, p<0.05) before SCT. The SOC mean value was not significantly associated with either the anxiety or the depression subscale.

Few significant differences were observed between subgroups formed based on nonresponse rate and sex; there was no systematic pattern of association between the nonresponse rate and gender across the different subgroups.

In summary, social and role function were the areas patients reported most deficits. The symptoms most frequently reported as problematic were fatigue, appetite loss, dyspnoea and a difficult financial circumstance. The highest levels of symptoms and impairments in function were reported six months after SCT, i.e. at the time of the first follow-up. Ratings of anxiety and depression were relatively high before SCT. The levels declined over time though not significantly so. SOC was related to the ratings of social and role function in the sense that those with a low SOC also scored their function as worse.

## PAPER II

The mean value on the intrusion scale was 16.6 (SD 10.0) before SCT, 10.2 (SD 6.4) at the first follow-up and 12.3 (SD 5.8) at the second follow-up. The corresponding mean scores for the avoidance subscale were 15.8 (SD 9.0) 11.4 (SD 8.8) and 12.1 (SD 9.6). Only one significant change over time was recorded: the mean of the intrusion scale decreased (p<0.05) between SCT and the two follow-ups.

Approximately half of the patients (n=9) reported scores above the cut-off point of 20, indicating a high stress response level on the intrusion scale before SCT. More than half of the patients at each assessment scored medium or high values. In the avoidance subscale seven of the patients evidenced a high level of distress before SCT. At the first and second follow-ups, the corresponding figures were two and three, respectively. A medium level of distress on the avoidance subscale was reported by eight patients before SCT, by six patients at the first follow-up and by four patients at the second follow-up.

The intrusion subscale correlated significantly to anxiety and depression on all three assessments (i.e. before SCT and at the two follow-ups). The correlations between intrusion and anxiety ranged from r=0.66 to r=0.68 (p<0.01). The corresponding figures for the depression subscale ranged from r=0.56 (p<0.01) before SCT to r= 0.62 (p<0.05) at the second follow-up. Concerning the relations between EORTC QLQ-C30 and IES, the strongest associations were found between intrusion and EF: before SCT r=-0.82 (p<0.001), at the first follow-up r=-0.54 (ns) and at the second follow-up r=-0.77 (p<0.01). Thus, the more self-rated intrusive symptoms reported by respondents, the greater were their self-rated anxiety and depression scores. In addition, the respondents' self-rated EF score was worse with a concomitant increase in self-rated intrusive symptoms.

## PAPER III

All patients who attended the interview completed the extended SEIQoL-DW. The median time for the HL survivors to complete the extended Swedish version was 37 minutes (range 15 to 115 minutes). The corresponding figure in the control group was 25 minutes (range 10 to 95 minutes). Overall, the respondents found it easy to respond to the questions and it was judged that the information collected was valid.

The median time from the HL diagnosis to the time of the interview was 14 years (range 6-26 years). The areas that were nominated as the most important in the life were family, personal health, work and relations to other people. Leisure ($p<0.01$) and finance ($p<0.05$) were the only areas that significantly differed between the HL survivors and the control group, with the former group nominating these areas less frequently. No significant differences were found between the ratings of the HL survivors and the ratings of the controls regarding satisfaction in each of the areas. The QoL global index score did not differ between the HL survivors (5.4, SD 0.9) and the controls (5.3, SD 0.7).

Thirteen respondents nominated five areas, 10 four areas, 23 three areas, 24 two areas, 24 one area that they believed were significantly influenced by HL and were consequently important in their life; 27 of the respondents did not mention any area that they thought was affected in some way by HL. Concerns about disease (13%), fatigue and loss of energy (11%) and late effects on skin and mucous membrane (11%) were the most commonly reported problems following HL. Forty-eight percent of the respondents reported at least one health aspect as influencing their current life situation. A change in their view of life and of themselves was reported by 66% of the survivors. An example of a statement categorized as such is the following: *I am more serious. I am still a clown but not as much as before. It feels as if I have grown more mature but it can be my age.* An example of a statement included in the category "Relations to other people" (mentioned by 15%) is as follows: *Friends disappear after a cancer diagnosis because of their own fear. You are treated as if you had pest.* Next, is an example of a statement included in the category "Thoughts and worries around disease": *Sometimes I think about the disease and wonder if it will return. It can pop-up when I'm about to go to bed. Sometimes I check my lymph glands. But I probably have to live with it.* Only nine percent reported family life and seven percent work as domains influenced by HL. The following is an illustration of a statement included in the category "Family": *It has had an influence at home. My husband has been ashamed over my disease. My children were teenagers and my 15-year-old daughter was ashamed.* An example of a statement concerning the category "Work" is: *I have another attitude. Status and work mean less while family and health mean more.*

Demographic and disease characteristics did not influence the ratings of the chosen areas among the HL survivors. Within the control group was age and sex not significantly related to the ratings of the areas considered as important.

## PAPER IV

No differences in the mean scores of the SEIQoL-DW index scores, HAD, SOC and MCS of the SF-12 were noted between the HL survivors and the controls. Only the PCS of the SF-12 differed significantly ($p<0.01$), where the patients (M=48.4, SD 10.4) reported being in poorer physical health than the controls (M=51.5, SD 8.3). The effect size of the difference was 0.37.

Twenty-seven (22%) respondents of the total sample of HL survivors (n=121) that were approached with the SEIQoL-DW did not report HL as influencing any area. Ten respondents did not participate in the weighting procedure. The main reason for not using the weighting procedure was that only two areas were nominated as being influenced by HL and the respondent did not find it meaningful to weight them. Thus, 84 of the 121 HL survivors were included in the final analyses. Partial correlation coefficients when controlling for age and sex between the measured variables in the HL survivors and the controls were calculated. The results were interpreted using Wilson and Cleary's HRQL model (Figure 3). The correlations differed significantly between the two groups on two occasions: Financial situation and MCS (z=2.1, $p<0.05$), and PCS and the QoL global index (z=2.7, $p<0.01$). Thus, HL survivors' rating a poorer mental health also rate their financial situation as poorer compared with the controls.

The results of the multiple regression analyses performed with the QoL global index as the dependent variables are presented in Table 7. The measured variables having the great-

**Table 7.** Multiple regression analyses with QoL global index of the SEIQoL-DW as the dependent variable

| Predictors | HL survivors and controls (n=335) β | | Controls (n=223) β | | HL survivors (n=78) β |
|---|---|---|---|---|---|
| | MCS, SF-12 0.38*** | MCS, SF-12 0.39*** | | MCS, SF-12 | 0.31** |
| | PCS, SF-12 0.27*** | PCS, SF-12 0.23*** | | PCS, SF-12 | 0.29** |
| | SOC 0.17** | SOC 0.17* | | SOC | 0.18 |
| | Age 0.04 | Age 0.05 | | Disease index | 0.26* |
| | Sex[a] -0.07 | Sex[a] -0.06 | | Age | 0.15 |
| | Survivorship[b] 0.09 | | | Sex[a] | -0.04 |
| | | | | Time since diagnosis | -0.02 |
| | | | | Disease stage | 0.03 |
| R² | .31*** | .27*** | | .54*** | |

β are standardized regression coefficients.
[a] Woman=1, man=2; [b] Control group =1, HL survivors=2
* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$

est impact on the QoL global index was mental health, physical health, SOC and the disease index in the HL survivors.

## FRAMEWORK OF THESIS

The results of the evaluation of the weighting procedure in the SEIQoL-DW gave no evidence that weighting had an impact on the results. When the SOC, SF-12 and HAD scales were correlated to the QoL global index and to the sum of the ratings (without the weighting procedure), the difference between using the weighting procedure was, on average, only .03 (range 0-0.07). A multiple regression analysis showed that satisfaction of the chosen areas explained nearly 90% of the variance in the QoL global index (standardized $\beta$ coefficient 0.94, $R^2$ 0.89, $p < 0.0001$).

# DISCUSSION

## HEALTH-RELATED QUALITY OF LIFE IN PATIENTS UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION

MORE THAN HALF of the patients undergoing autologous SCT reported a rather good HRQL both before and up to one year after SCT. However, some patients experienced impaired function, physical symptoms and emotional stress. When the first two studies of this thesis were conducted (1992-1993), there was only one prospective study published focused on this group of patients (Chao et al. 1992). The situation is quite different today, where there are a large number of reports having a prospective design (Chao et al. 1992, Syrjala et al. 1993, Meyers et al. 1994, Andrykowski et al. 1995, McQuellon et al. 1998, Baker et al. 1999, Hjermstad et al. 1999b, Hjermstad et al. 1999c). The findings in the current study are consistent with those of other reports indicating that the most physically stressful period for patients is approximately 3-6 months after SCT. The majority of investigations in patients undergoing SCT show enhanced anxiety and depression, with the higher levels before transplant and during hospitalization, a finding that was confirmed in the present study (Syrjala et al. 1993, Jenkins et al. 1994, Meyers et al. 1994, Andrykowski et al. 1995, Leigh et al. 1995, Hjermstad et al. 1999c). However, the definition of "case" according to the HAD may not necessarily indicate psychopathology, but might reflect a prolonged process of recovery (Hjermstad et al. 1999c). Most of these patients had already received chemotherapy for their blood disorder before the high-dose treatment and subsequent autologous SCT (data not published). This may partly account for the high percentage of cases of depression (30%) detected before SCT in our study. Nevertheless, patients undergoing autologous SCT have a risk of developing anxiety and depressive symptoms.

When this study was published it was not possible to compare the results to Swedish norm values. Today, however, methods have been introduced to evaluate clinical meaningfulness, which can serve to improve interpretation of HRQL results in clinical studies (King 1996, Hjermstad et al. 1998, Sprangers 2002). When the patients that underwent autologous SCT were compared with a norm group adjusted for age and gender, the findings of the EORTC QLQ-C30 presented in the framework of this thesis were strengthened. The impairments recorded in the functional scales, however, appear to be even greater than those presented in Paper I. Other studies that have made comparisons with general norm groups have reported survivors as being restricted in physical functioning, social functioning and role functioning (Syrjala et al. 1993, Prieto et al. 1996, Sutherland et al. 1997, Hjermstad et al. 1999a).

An impressive number of studies have been carried out in this group of patients even if many of these studies have certain methodological weaknesses. The patient samples are in some studies heterogeneous, including patients with different diagnosis, which makes it difficult to draw conclusions on what impact a specific diagnosis has on HRQL. Furthermore, many studies have used a retrospective design with varying follow-up times. Thus, it is difficult to draw any firm conclusions as to the exact impact the treatment has had on HRQL. The body of knowledge on how these patients perceive their HRQL is sufficiently large to suggest that interventions are initiated and systematically evaluated. Interventions could be directed toward areas of HRQL, where the care can be improved. For instance, such an area could be directed toward eating problems and oral mucositis with the development of nursing care. It is also suggested that a nurse specializing in psychosocial oncology be attached to departments treating patients with malignant blood disorders. With a combined medical and psychosocial education such a nurse is highly suitable for supporting patients, relatives and other staff members (Wettergren et al. 1996). This nurse can organize practice according to the needs of the patients and the department. In this way, counselling could be offered to patients during treatment and rehabilitation and, when appropriate, the nurse could refer patients to psychological services (Sheard and Maguire 1999, Fallowfield et al. 2001). Furthermore, patients and family members should be informed that reduced physical functioning and emotional distress is normal, not only during the acute phase and post-transplant period, but also during the first year of recovery. Emotional disruptions may be more easily tolerated if they are recognized as normal reactions and similar to those experienced by other patients in the same situation (Massie and Holland 1989). Another area of growing importance for patients undergoing high-dose treatment followed by SCT and in cancer patients in general is financial difficulties due to the patients' disease and prolonged treatment (McQuellon et al. 1998, Baker et al. 1999, Hjermstad et al. 1999a, Michelson et al. 2000).

## HEALTH-RELATED QUALITY OF LIFE IN SURVIVORS OF HODGKIN'S LYMPHOMA

The overall impression is that the long-term survivors of HL in this study have adapted to their new life situation exceedingly well (Wettergren et al. in press). Anxiety, depression, mental health and the individual rating of general QoL of the HL patients did not differ from those of the control group. However, it is noteworthy that a sizable proportion of the patients had already died because of disease and its treatment. Among the HL survivors who actually participated in the study, only one significant difference was detected between the patient sample and the control group, namely that, the HL survivors reported a poorer physical health than the controls. This finding is in accordance with the results of a limited number of studies in HL survivors that compare HL survivors with a randomly selected control group from the general population. In these studies restrictions in physical health and fatigue have been reported (Joly et al. 1996, Loge et al. 1999, Loge et al. 1999).

The extended version of SEIQoL-DW used in the current study also includes a disease-specific module that is intended to capture the respondent's health-related QoL as well as both negative and positive aspects of having had a disease. When the participants were asked what impact HL had on their life, 67% reported at least one health problem. However, only 47% ranked this as important, leaving 20% with some health concern that affected their life, but that was not considered important. Furthermore, in contrast to the other studies, the present study revealed a lower percentage of fertility concerns (Fobair et al. 1986, van Tulder et al. 1994, Joly et al. 1996, Abrahamsen et al. 1998), fatigue (Fobair et al. 1986, Bloom et al. 1993, Loge et al. 1999) and work-related problems (Fobair et al. 1986, Bloom et al. 1993, Abrahamsen et al. 1998). There is no obvious explanation to this discrepancy in results. One explanation could be that the extended SEIQoL-DW captures the patients' view on how tolerable the concern is rather than only the presence of symptoms or level of functioning. If a patient has adapted to a changed life situation, for example a new job or childlessness, a standardized questionnaire would probably register this as a deficit, while the extended SEIQoL-DW may only record it if the patient perceives the affected area as important. However, the patient might have deficits that she/he does not see as related to HL. Furthermore, some areas such as sex life may be left out, as they might be perceived as embarrassing.

The domain that was most frequently reported as important and crucial for QoL in both HL survivors and controls was the family. A similar finding was reported in a recent study that also included the SEIQoL-DW in patients with hematological malignancies (Montgomery et al. 2002). Because the family is viewed as an important element in patient's life it is suggested that family members (and close friends) become involved in the care of patients with malignant blood disorders.

When the results of the study were illustrated in the conceptual model many factors, such as disease stage at diagnosis, SOC and financial situation, influence the perception of HRQL and are important to include in evaluations of HRQL in patients with malignant blood disorders. The most important determinants of perception of overall QoL were self-rated physical and mental health as well as SOC. This study supports the multidimensionality of the concept of QoL and highlights the complexity of interpreting measurements of HRQL. It is therefore not enough to summarize HL survivors' HRQL by evaluating their physical impairments, on should also include an evaluation of their mental state, emotional distress, coping capacity and how the respondents that report restrictions value these deficits. Furthermore, terms such as symptom status and health status should not be used synonymously with QoL, as has been done previously (Smith et al. 1999).

Disease stage at diagnosis was only weakly associated with the reported symptoms. The weak associations between disease characteristics and symptom status may be due to the selection of HL survivors, being diagnosed at the minimum five years earlier. The time factor may have had a stronger influence on symptom status closer to diagnosis and treatment.

We suggest the model of Wilson & Cleary could be used for the choice of study design and instruments in research and as well as for an explanation of research results. What is more, the model may be useful when developing intervention programs and rehabilitation

for HL survivors. Finally, the model can serve as a tool for evaluation by indicating what kind of measures to use.

The measures chosen for this study nicely fitted Wilson and Cleary's HRQL model and it was found to be fruitful for analyses of the results. Nonetheless, further research is required to evaluate if the chosen measures are the most appropriate.

## SWEDISH VERSION OF THE SEIQOL-DW

This study is one of the first to include analysis using the Swedish extended version of the SEIQoL-DW. The results support the construct validity of both the disease index and the QoL global index as the correlation between these two scores is moderate and the correlations with the mean scores of the standardized instruments included are all in the expected direction. The instrument may also have important clinical implications in evaluation of patients in giving an opportunity to speak about how they perceive their current life situation. The question, *"If you think about the fact that you have been treated for HL, what in your life is influenced, both positively and negatively, by this event?"* gives patients an opportunity to reflect upon their condition and to report their personal opinion on what impact the disease has had on their life. Interestingly, the most commonly reported impact of disease, was a change in their view of life and of themselves, reported by 66% of the survivors. The patients' response to this question is highly crucial for caregivers as well as researchers. The method for measurement in the SEIQoL-DW captures the patient's perspective of life and health, in line with most definitions of the concept of HRQL (Calman 1984, Cella 1992, Bowling 1997). As most QoL definitions state that it is multi-dimensional and unique for every individual, a valid measure should logically be based on each individual's own areas of importance and an evaluation (rating) of these areas (Calman 1984, O'Boyle 1994, Bowling 1995).

There are, however, some parts of the extended Swedish version of SEIQoL-DW that should be further evaluated and eventually revised and improved.

Firstly, the results of the analysis of the weighting procedure needs be discussed. The results revealed that the global QoL scores are being largely 'driven' by the satisfaction ratings (Likert scale), with the importance ratings (e.g. the weighting with the disc) having only a minor role. The difficulties of interpretation of combined satisfaction and importance ratings have been recently been demonstrated (Trauer and Mackinnon 2001). Even if the weighting procedure does not add much at the group level, it can be valuable at the individual level by identifying areas that are especially important to the individual patient. In addition, the disease-specific module of the SEIQoL-DW allows one to discuss exactly what is troublesome and what the patient holds as most important.

Secondly, the rating of satisfaction may sometimes be difficult to perform with the disease-specific module of the SEIQoL-DW. Because respondents reported both positive and negative aspects, the rating of the chosen area may be difficult. For instance, when rating a change in evaluation of life, it is understandable to ask how satisfying this is now. But when rating a negative aspect, such as loss of teeth, the question has to be formulated differently

to accommodate the problem for the patient. The question could then be revised to read, "How do you get along despite your loss of teeth? This methodology needs to be further evaluated.

Thirdly, it can be questioned if the disease-specific module is an entirely comprehensive measure of symptom status. Concerning the affect that HL has on the respondents today, the respondents are asked to report both positive and negative aspects of the disease. This request opens up the possibility of bringing up both complications as well as any, and positive aspects of the disease. Some problems may not be present on the day of the interview and therefore will most likely not be included in the protocol. An example could be difficulties in sleeping or fatigue, which may be forgotten after a good night's sleep. Other complications, such as sexual problems and infertility, may be embarrassing to speak about and therefore are not taken up by the respondents. It is therefore recommended that a standardized measure of symptom status should be included in future studies in order to further evaluate and test the disease index of the extended SEIQoL-DW.


## METHODOLOGICAL CONSIDERATIONS

A major limitation in the first study (Papers I and II) is the small sample size, which must be kept in mind when interpreting the results. In addition, the results may be biased by the fact that the condition of several patients worsened and some died during the course of the study. It is well known that it can be difficult to obtain large samples when performing clinical studies in small specialty areas. Subgroup analysis is difficult with a small sample, such as sex, diagnosis and "case" of anxiety or depression.  These circumstances may have contributed to the present lack of statistically significant findings. Longitudinal studies of HRQL in patients with advanced cancer may result in nonrandom missing data because of death and deteriorating health. It has been noted that a failure to recognize the problem of missing data based on death and deteriorating health can lead to a better evaluation of patient HRQL (Moinpour et al. 2000). In order to minimize this threat, descriptive data should include all patients who complete the questionnaires at each assessment. Analysis over time, on the other hand, includes only patients who have participated on all three occasions. Furthermore, we tested to determine if those who failed to complete the study differed in their perceptions of HRQL before SCT from those who became nonresponders during the study. The results indicated no difference between nonresponders and those who failed to complete the study.

A large number of statistical tests have been performed in the first two Papers (I and II). This increases the risk of obtaining significant results by chance, i.e. to commit a type I error, i.e. an error made by wrongly rejecting a true null hypothesis. However, this problem can be counteracted by using a more stringent p value, which would cause an over-correction of type I errors.  The risk for type II errors, an error made by wrongly accepting (or failing to reject) a false null hypothesis, was seen as highly probable and thus the p value was set at <0.05. The findings were mostly consistent with earlier research and isolated significant results were not highlighted because they were not considered relevant to the study.

The proportion of HL survivors and controls completing the study (Papers III and IV) were small and is seen as a limitation of the study. When the study was designed, a statistician was consulted for selection of the control group. Based on the nature of the personal interview that took place at the Karolinska Hospital, a response rate of about 50% was expected. In analyzing our method for selection of controls, maybe some other technique should have been used. It is, however, a difficult problem in clinical research to induce the general population to participate in an interview takes considerable time and effort to complete and where the only financial reward is a movie ticket. When a similar study was performed in Great Britain, the interviewers visited the respondents in their homes to conduct the interviews (Bowling 1995). That study obtained an acceptable response rate of 77%.

The attrition rate has been evaluated to analyze its possible consequences on the internal validity of the study. Our control group did not differ from the general population in Stockholm County regarding percentage employed (Official Statistics, 1999). Further, our controls reported the presence of a long-standing illness at the time of the interview (unpublished data) to the same extent as the official statistics for the general population. Having a long-standing illness is interpreted as an indicator of reduced physical function (Michelson et al. 2000). Such reductions are well described in HL survivors (van Tulder et al. 1994, Joly et al. 1996, Loge et al. 1999). Although only Swedish citizens were allocated to the control group, one might suspect a bias regarding ethnicity (Kreiger and Nishri 1997). There were more surnames with a foreign origin in nonresponders than in responders in the control group. Almost no respondents (HL survivors or controls) who were interviewed had difficulties using the Swedish language. A possible explanation is that persons may feel uncomfortable in attending an interview if they are not proficient in the language being used. Interviewers fluent in other languages have been suggested to decrease refusals attributed to language difficulties (Kreiger and Nishri 1997). In the present study it is not possible to see a distinct pattern of compliance as a function of the patients or controls' residential area.

Overall, bias because of the high attrition rate cannot be ruled out. The results of the control group should therefore be treated with caution when interpreted in terms of a 'Swedish norm'. Nevertheless, the controls are seen as representative for comparison with the HL survivors in the sense that both samples are likely to suffer from the same biases.

It is suggested that the SEIQoL-DW should be evaluated for its use as a questionnaire tool for patients. The questionnaire could then be sent to participants and the method tested in a larger population, especially in that the support for the weighting procedure is weak, which was the main reason for a personal interview.

# SUMMARY AND CONCLUSIONS

THE MAJORITY OF the patients with malignant blood disorders report a rather good functioning during the first years following autologous SCT. The most impaired area of functioning was social function, both before and after SCT. The symptoms most frequently reported as problematic were fatigue, appetite loss, dyspnoea and a difficult financial circumstance. High levels of post-traumatic stress symptoms were recorded which were related to higher emotional distress, which emphasizes the importance of psychosocial care for this group of patients. A part from improvements in medical management, psychosocial expertise is suggested to be available at all centers. Such a resource, a specialized nurse, has been established at our center.

Long-term survivors (>5 years) of HL perceived their general QoL as good and comparable to that of a control group even though they reported their physical health as worse compared to the control group. The most important domains in life (>50% of patients and controls) that were seen as crucial for QoL, were family, personal health, work and relations to other people. Thoughts and worries concerning disease, fatigue and loss of energy and late effects on skin and mucous membrane were the most commonly reported problems of importance following HL. Sixty-six percent of the survivors reported a change in their view of life and of themselves. Overall, long-term survivors of HL seem to have adapted well to life. Hopefully recently risk adapted treatment strategies will reduce impairments in physical health in the future.

This initial validation of the extended Swedish version of SEIQoL-DW was found to be a valuable tool in the evaluation of HRQL in HL survivors and controls. The results are interesting in revealing both positive and negative aspects of the disease and its treatment. Further research is however needed regarding the psychometric properties.

HRQL is complex and the interaction of many factors, such as disease stage, SOC and the financial situation, that need to be taken into consideration when evaluations are conducted. It is suggested that the model such of Wilson and Cleary could be used in selecting study design and choosing instruments in research as well as for interpretation of results.

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