Thesis for doctoral degree (Ph.D.) 2009

QUALITY OF LIFE AND HEALTH FOLLOWING ALLOGENEIC SCT IN CHILDHOOD

Catharina M Löf

Thesis for doctoral degree (Ph.D.)
2009

QUALITY OF LIFE AN HEALTH

FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION IN CHILDHOOD

Catharina M Löf

Karolinska Institutet

Karolinska Institutet

Department of Clinical Science, Intervention and Technology,
(CLINTEC)
Division of Paediatrics, Karolinska Institutet, Stockholm, Sweden
Karolinska University Hospital Huddinge

QUALITY OF LIFE AND HEALTH FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION IN CHILDHOOD

Catharina M Löf

Fil.mag

Karolinska Institutet

Stockholm 2009

Published by Karolinska Institutet.

ISBN 978-91-7409-689-7

Printed by
REPROPRINT AB
Stockholm 2009
www.reproprint.se
Gårdsvägen 4, 169 70 Solna

To all the children, and their families, who have undergone stem cell transplantation

ABSTRACT

Hematopoietic stem cell transplantation (SCT) is curative in refractory leukaemia and in several other haematological and immunological disorders. However, SCT is associated with morbidity and mortality and entails major strains on children and their families. The survivors often have life–long somatic and psychological late effects to contend with. The overall objective oft this study was to gain knowledge of these children's life situation, health related quality of life (HRQoL) and health following SCT. All parts of the study have a cross-sectional design to evaluate self- and proxy-rated HRQoL and health. Clinical record data was compiled to investigate the relationship between the patients` medical condition and the self-rated situation. Self-rated health was reported in a symptom inventory checklist. Generic questionnaires were used to survey HRQoL and health: the Swedish Child Health Questionnaire SCHQ-CF87 (children) and -PF50 (parents), SWED-QUAL (adults), I Think I am, Sence of Coherence-13 and HAD (adults). Physical functional status was assessed using Lansky and Karnofsky scales. Socioeconomic issues were included in the last study. Initially, a consecutive sample of children (n=52, age >9 years) who were at least 3 years after SCT was studied. The second and third parts of the study also included their parents (n=42). Study four and five described adults who had undergone SCT as children (n=53, age >19) and who were at least five years after SCT. As a group, children had good self reported HRQOL compared to norm and to other chronically ill children. No correlation was found between the physician-rated degree of late effects and overall HRQOL. Contrarily, HRQOL was related to the degree of self-rated symptoms. Children with leukaemia, severe chronic GvHD or cognitive deficits had lower HRQoL. Parent proxy QoL scores tended to be lower than children's own scores .The level of late effects or of subjective symptoms was associated with a lower parental rating of the child's HRQoL. The child's condition impacted on the parents' emotional situation. Clarity with regard to who is responsible for assessing the child's HRQoL is thus crucial, and so are complementing perspectives. The adult survivors after paediatric SCT perceived a poorer HRQoL than norm, but a relatively good health. HRQoL and health improved with age, although severe psychological and cognitive problems are common. A majority was troubled by infertility and had not received sufficient advice in sexual matters. Adult survivors lead fairly normal lives, but an important subgroup encounters more difficulties, with a lower educational level, psychological ill health and a poorer financial situation, particularly among the younger and women. It is emphasized that medical follow-up should be integrated with psychosocial and neuropsychological support including advice in sexuality and fertility issues, when patients enter adulthood.

Keywords: children, SCT, HRQoL, health, long-term, late effect, psychosocial, socioeconomic

Kort sammanfattning (svenska)

Med hjälp av allogen stamcellstransplantation (SCT) kan numera barn med refraktära leukemier och andra livshotande hematologiska och immunologiska sjukdomar i många fall uppnå bot. SCT är fortfarande en besvärlig, riskfylld metod, förenad med en viss dödlighet. De patienter som överlever har ofta både somatiska och psykologiska seneffekter som följer dem hela livet. Det övergripande syftet med denna studie var att få ökad kunskap om livssituationen för de barn som genomgått SCT, främst med fokus på deras livskvalitet och hälsa. För att få en bild av deras självskattade och proxyskattade situation har vi använt en tvärsnittsdesign i alla fem delarbetena. Patientens medicinska status enligt journaldata jämfördes med den självupplevda situationen. Självskattad hälsa mättes med en SCT-specifik symptomenkät. Den hälsorelaterad livskvaliteten (HRQoL) och hälsan studerades med de multidimensionella instrumenten Swedish Child Health Questionnaire SCHQ-CF87 (barnen) och -PF50 (föräldrarna), SWED-QUAL (vuxna), Jag tycker Jag är, Känsla av sammahang-13 och HAD (vuxna). Den fysiska funktionsnivån skattades med Lansky och Karnofsky skalorna. Den socioekonomiska situationen undersöktes med frågor från ”Undersökning av levnadsförhållanden”(SCB) (vuxna) Den första delstudien innefattar en representativ studiegrupp med barn (n= 52, ålder >9 år) som hade genomgått SCT minst tre år tidigare. I den andra och tredje delstudien deltog också barnens föräldrar (n = 42). Studie IV och V belyser situationen för de vuxna som genomgick SCT som barn (n= 53, ålder >19 år) minst fem år tidigare. Barnen rapporterade själva att de hade en god livskvalitet jämfört med norm eller andra kroniskt sjuka barn. Barnens HRQoL hade främst samband med den självrapporterade hälsan och korrelerade inte överlag med de objektiva medicinska seneffekterna. Barn med leukemi, allvarlig GvHD eller stora kognitiva svårigheter hade dock en sämre HRQoL. Föräldrarnas proxyskattade HRQoL låg lägre än barnens egen skattning, och låga värden korrelerade till en högre grad av seneffekter eller självrapporterade symptom hos barnet. Barnets tillstånd påverkade också föräldrarna emotionellt. Det är därför viktigt att urskilja vem det är som bedömer barnets livskvalitet, men också att barnens och föräldrarnas perspektiv får komplettera varandra. De vuxna som hade genomgått SCT under barndomen upplevde en lägre HRQoL än norm, men hade en överlag relativt god hälsa. Med ökad ålder rapporterades både bättre HRQoL och hälsa, dock var det vanligt med svårare psykiska och kognitiva besvär. En majoritet upplevde problem rörande infertilitet, och de hade saknat information och stöd gällande sexuella frågor. En majoritet av de vuxna långtidsöverlevande lever ändå relativt normala liv. Men det finns en viktig mindre grupp som behöver uppmärksammas som har mer svårigheter; med låg utbildningsnivå, psykiska besvär och en sämre ekonomisk situation. Detta gäller framförallt bland de yngre och kvinnorna. För den unga patienten som är på väg att bli vuxen bör den medicinska uppföljningen integreras med ett psykosocialt- och neuropsykologiskt stöd, som dessutom innefattar information om fertilitet och sexualitet.

Nyckelord: barn, SCT, HRQoL, hälsa, långtids, sen effekter, psykosocial, socioekonomisk

LIST OF PUBLICATIONS

ORIGINAL PAPERS I-V

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

I

Forinder U, Lof C, Winiarski J. Quality of life and health in children following allogeneic SCT. *Bone Marrow Transplantation* 2005; **36**(2)**:** 171-176.

II

Forinder U, Lof C, Winiarski J. Quality of life following allogeneic stem cell transplantation, comparing parents' and children's perspective. *Pediatric Transplantation* 2006; **10**(4)**:** 491-496.

III

Lof CM, Forinder U, Winiarski J. Risk factors for lower health-related QoL after allogeneic stem cell transplantation in children. *Pediatric Transplantation* 2007; **11**(2)**:** 145-151.

IV

Löf CM, Winiarski J, Giesecke A, Ljungman P and Forinder U. Health- related quality of life in adult survivors after pediatric allo-SCT. *Bone Marrow Transplantation* 2009;**43**,461-468.

V

Löf CM, Winiarski J, Ljungman P, Forinder U. The socioeconomic and psychosocial circumstances of adult, long-term survivors of allogeneic stem cell transplantation in childhood or adolescence. (*Manuscript)*

CONTENTS

LIST OF ABBREVIATIONS

AML	Acute myeloid leukaemia
ALL	Acute lymphoblastic leukaemia
GvHD	Graft-versus-Host Disease
HAD	Hospital Anxiety and Depression scale
HLA	Human Leukocyte Antigen (The human major histocompatibility locus)
HRQoL	Health Related Quality of Life
ITIA	"I Think I am" self report instrument assessing selfesteem
QoL	Quality of Life
SOC	Sense of Coherence
SCT	Allogeneic stem cell transplantation
PRO	Patient Reported outcome
ULF	Swedish Living Condition Survey
SCHQ	Swedish Child Health Questionnaire

BACKGROUND

Research focusing on aspects of the quality of life has increased considerably over the last few decades, especially within medical research with the aim of evaluating the effects of treatment and disease impact (1). Quality of life semantically speaking means ”the essence of existence” or the values that are central to life (2). Most people in western society are generally acquainted with the expression ”quality of life”, and most have an intuitive understanding what it means (3).

THE CONCEPT OF QUALITY OF LIFE

Quality of life is an organizing concept, a construct that can be used as a guide to its users (4). Quality of life (QoL) is discussed from different angles in the various scientific disciplines, most of all in philosophy, psychology, medicine, sociology and economics (3-5). In philosophical parlance we can choose to understand the term as a pure ”term of value” (5). QoL from a philosophical standpoint is said to be ”the good life” or touches on existential questions. Somewhat simplified you could say that a person’s quality of life is high if and only if she has a good life, and if the quality of life is low that she has a bad life. It is not the same as high quality of life meaning a higher moral life style or a more aesthetically attractive life but more that the person in question feels good, lives a life which is good for herself and largely a life worth living. Similarly it means that if a person’s quality of life is low, her life is bad for herself, e.g. that the person lives a poor or plain life (5). In psychology, QoL is related to mental states which recently have gone over to being described in terms of psychological well-being (2). In sociology, QoL is included as part of the concept of welfare and in economic science, QoL is connected to the GDP product e.g. in order to measure the distribution of a population’s prosperity (2). In medical science, QoL and objective and/or subjective health are connected, which is expressed as ”health-related quality of life” (HRQoL) (4). In the following text the abbreviation HRQoL is used for the health-related quality of life concept.

HRQoL ”Health-related Quality of Life”

The term HRQoL is used in a medical context in evaluation research, as ”outcome research” in order to measure the effectiveness of different treatment forms and disease impact (4, 6). The traditional evaluation measurements are being complemented these

days by making appraisals of the effects a treatment has on the patient's life as a whole (7). The multi-dimensional thinking behind health and wellbeing dominant in HRQoL research originates mostly from the World Health Organization's Declaration of Health dating back to 1946 (8). This definition highlighted and emphasized the importance of the physical, mental and social dimensions in connection with illness and disability. During the 1990s the WHO's Quality of Life Group (WHOQOL, World Health Organization Quality of Life Group) further developed the Declaration of Health with a definition of the quality of life as "an individual's perception of their position in life in the contexts of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"(9). This is a broad concept which is influenced by the individual's physical health and psychological state, level of dependency, social relations and relations to tangible events in their close environment.

The concept of quality of life (QoL) and HRQoL are still vaguely defined concepts and they have as yet no universally accepted definition (3, 7). There is an ongoing discussion within QoL research about the necessity of clarifying the distinctions between QoL, HRQoL, health and functioning level. HRQoL can be regarded as a narrower area and a part of QoL (3, 7). In turn health can be regarded as a part of the HRQoL area. The concept comprises many fields, everything from physical functioning to family situation, relationships to others, psychosocial situation, social support, sexuality to spirituality (3, 4, 7). Other definitions in medical research highlight the difference between the expectations the patient has of life and HRQoL, and on the actual experiences of it, and experience of their life situation (1, 10, 11). Studying and analyzing HRQoL is not without its problems when we bunch several different factors together such as e.g. physical symptoms, emotional well-being and social and cognitive functioning (5). It is central to make an operationalization of the concept when conducting a study (1, 7). Although, HRQoL as a hypothesized construct can never fully be operationalized by its measurements, instead it should be seen as an indicator to the underlying construct (4). However there is consensus on some of the aspects to consider in HRQoL research as regards both children and adults (4, 12)
; A) HRQoL is a multi-dimensional field and instruments to encompass this must include the four core areas for HRQoL i.e. disease status, physical, psychological and social functioning. B) as it is a multi-dimensional area there should be values for each area rather than a global summation of the values. C) HRQoL instruments must

have high validity and high reliability. Concerning children, it is also important that the instruments are brief, easy-to-administer and analyze, and be norm giving with children who have different levels of difficulties in their disease and treatment (1, 4). It is important for both children and adults to differentiate between different levels of illness and the degree of functioning and preferably encompass the frequency of problems than only assessing the individual's capacity (12).

Theories and models of HRQoL

There are several conceptual models trying to explain the relationship of patient reported outcome (PRO) of HRQoL (1, 2, 7, 13, 14). A frequently used model that tries to explain the causal relationship that influences self-reported health and HRQoL is Clery and Wilson's conceptual model (13). Specific physiological processes, symptoms and functional status form a causal chain to PRO. But also this model brings clarity to the underlying factors (individual and environmental characteristics) that have an important influence on this causal chain (13).

The utility model comes from the economic decision theory and is used for comparing different treatments based on the patient-based subjective perception of effects of medical treatment (15). This model can be used as a basis for policy decisions in the health care sector. The person is asked to imagine a specific health condition and express how she experiences her situation and based on her answers; decisions are taken on the quantity and quality in her life. In short, the person is asked about what is most or least attractive; a shorter life with fewer disabilities or a longer life with more physical disabilities, - this is quantified as Quality Adjusted Life Years (QALYs) (15). This model has been criticized as unusable in pediatrics, because children find it hard to understand and formulate abstract thoughts about deciding on quality and quantity in life (12). Two other theories have been identified in a review concerning the conceptual underpinnings of HRQoL measurements' in children (1); The discrepancy theory (10) and Lindstrom's model of QoL (16). The discrepancy theory essentially means that a poor QoL is the result of discrepancies between an individual's actual self and ideal self ("like me" and "how I would like to be")(10). This theory is however criticized for not being useful in providing directions for intervention to increase children's HRQoL (1). Lindstrom's model of QoL considers both macro and micro aspects of QoL that are applicable on children (16). This model expresses four spheres of human existence: global (ecological, societal, and political), external (social and economic resources) interpersonal (social relationships and supports) and lastly a personal sphere (physical,

mental and spiritual aspects). This mirrors the criticism about the difference between models and theoretical starting points: is it appropriate to measure HRQoL with a summative index or should the focus be on the different parts which make up HRQoL (12). Many instruments are criticized however for building on an atheoretical basis and do not have a clearly defined HRQoL model to work from (1, 6).

In addition there are several practical approaches where HRQoL is used as a measurement of results (7): either a combination of several different instruments is used in order to measure the various HRQoL fields, or an instrument with different parts or part scales is used, or quite simply focusing on one or more areas of HRQoL (e.g. emotional well-being, physical level of functioning) (12). The criticism leveled at the first mentioned method is that the various instruments can be so different from a theoretical standpoint and then be weaker psychometrically (17, 18). Secondly the construction of the scales can differ widely between the instruments which bring weaknesses in the analysis of how different aspects of health and dysfunction affect these areas (7). Another approach are the individual assessment of QoL areas (IQoL), which makes it possible for the patient to spontaneously find the areas in life that are important for her quality of life (19) In short the individual's own definition of her quality of life is investigated "it is not merely what the patient says it is, but what he/she tells himself or herself what it is" (19).

Generally speaking one can say that there are two types of HRQoL instruments (4, 7, 20): general (generic) ones and disease-specific ones. Generic instruments are intended for use with different populations, both norm populations and groups with a disease. This means that the result can be compared over different groups regardless of the degree of seriousness of the disease or treatment given. The disadvantage with a general instrument could be that it loses its precision and sensitivity in the measurements to a particular patient group (7). Specific HRQoL instruments are designed for use with a limited group taking into account e.g. disease, functioning or a special population and which is of significant value clinically (7, 12, 14). The criticism of disease-specific questions is that it can be too narrow and not take other important aspects into account (other than the physical symptoms) that act as mediators to the patient's quality of life, or as strongly stated by Wallander et al. (4) not even be a measure of QoL. In 1993 WHO together with International Association for Child Psychology and Psychiatric Working Party proposed that new measures should be the

child-centered, use subjective self-reporting where possible, be age-related, have a generic core and specific modules and emphasize health-enhancing aspects of QoL (21). With an increasing interest in studies targeting children over recent decades, several HRQoL instruments for this particular group have been developed (1). The Child Health Questionnaire (CHQ) (22) is a generic HRQoL instrument frequently used in the Nordic countries, Europe and USA. The content for the CHQ was derived from previous pediatric measures and from observation and input from families, as well as developmental considerations of children such as competence in verbal comprehension (22). The theoretical starting point in the CHQ is based on WHO's definition of health (8). Also based on an ongoing discussion about the social dimension connected to health and well-being, the CHQ was constructed with a point of departure in two complementary dimensions: physical and social well-being (the latter includes emotional, behavioral and social well-being). The hypothesis is that a deficiency in any of these two dimensions probably has an effect on the child's ability to take part in social "roles" such as school work, family activities, and relationships with others. The model of the instrument is based on every dimension in HRQoL having to be measured according to three important cornerstones such as current status, limitations and self-reporting (23, 24). Another standardized generic instrument widely used in Nordic populations (25, 26) with children that focuses on one HRQoL area, the child's self esteem, is "I Think I am" (27). Taking into account developmental considerations, "I Think I am" has age-appropriate questionnaires with items and response formats dependent upon the developmental level of the child (27).

There are several instruments available to measure HRQoL/QoL in adult populations and studies have shown that generally approximately 5-15 dimensions are included (4). The Swedish Health-Related Quality of Life Questionnaire (SWED-QUAL) (28) is a generic Swedish questionnaire originally adapted from measures in a large US study "The Medical Outcome Study" (MOS) (29). SWED-QUAL is a validated instrument (28) and evidence of satisfactory psychometric properties has been reported for the scales when used in similar Swedish studies regarding HRQoL in adults (30) and in studies on other illness-related adult groups (31-34).

There are studies that emphasize the emotional impact of the disease or treatment and direct the study with a questionnaire concerning the psychological aspects. Hospital Anxiety and Depression scale (HAD) is one example of an instrument that was developed to measure the level of anxiety and depression in patients (35, 36). This instrument is widely used in cancer patients (37). Previous research with mostly cancer

patients who underwent treatment during their childhood and who are now adults has shown that this can be a problem area (38). There are recommendations for HAD with cut-off scores indicating possible clinical problems (37, 39).

Health

Health is another broadly defined concept that also tends to impinge on other concepts, like well-being, positive health and so on (6). This text only tries to make a conclusion of the health concept, and for further presentation and analysis, recent literature on the subject is recommended (11, 40, 41). Health is by definition a part of the HRQoL concept - an aspect of HRQoL (4, 9, 12). The most outstanding theme for definitions of health during the 1900s, and the 2000s, has been the biomedical and the humanist perspective (41). The biomedical perspective states that health is the absence of sickness, and that humans are biological systems of functioning organs. Hence, in simple terms, when the organs work normally, the person is in good health. From the humanist point of view it is health and not disease, and the relationship between these two that is emphasized. Health and sickness can be seen as a continuum or as different dimensions (41). The WHO Health Declaration (8), as previously mentioned, still has a strong influence on theoretical education within the area of health. To measure health and identify health problems in health care and population-based studies (in health economics studies among others), an index is used as a measurement which juxtaposes different factors such as mortality, morbidity and consequences of morbidity (42-44) (Hälsoindex ref). DALYs (Disability Adjusted Life Years) is an example of such an index, where years of life lost are juxtaposed with years with impaired functional ability (42). Global self-rating of health has proved to be a very reliable way of finding out about a patient's self-evaluated health and has strong links with predictive factors and identifies risk groups (45, 46). Age has proved to have a U-shaped correlation with health, where the oldest and the youngest age groups have the best self-reported health (46). While adults compare how their health status was before their illness, however, this comes in another light when a small child, who has no memory of good health to compare with, falls ill. Longitudinal studies in groups with chronic illnesses show that there can be a Response Shift i.e. that the individuals change their criteria for their health and give different answers to the question over time (47).

Mental Health

Another concept that is related to, and a part of, the HRQoL area is psychological health or mental health (4, 12). Psychological/mental health can be defined from a health perspective (salutogenic) or a disease perspective (pathogenic). The salutogenic perspective focuses on the individual's experience of their psychological health, their ability to adapt and deal with external trying situations (48).

Psychological ill-health is hard to define and ranges from psychiatric disease to troubles that cause personal suffering but which are not always assessed to be a psychiatric diagnosis - such as psychological difficulties (worry, anxiety, memory, concentration problems and sleeping problems) (49, 50). There are models explaining that the psychological state of the individual is influenced by three relationships – the biological/bodily constitution, the cognitive ability to understand and interpret the surroundings and ability to deal with these for optimal survival, and the design of the environment (49). When there is a balance between these three relationships, the individual can deal with everyday life without any trouble, but if the balance is disturbed in one or more of these, the psychological health of the individual is affected. Aspects of mental health have a stronger relationship to the individuals QoL than the self-reported health, which indicates that the respondent makes a distinction between these factors (51). In this thesis the psychological well-being of long term surviving paediatric SCT patients is examined from the patient's own subjective experience/view of her psychological health/ill-health through a series of questions about the positive/negative effects, anxiety, depression and cognitive troubles with memory and concentration.

HRQoL and socio-economic factors

There are still few clinical HRQoL studies that highlight how external factors such as education, employment, financial situation, for example, can influence PRO (Patient Reported Outcome) regarding health and well-being (6). A report from The Childhood Cancer Survivor Study (52) (US) indicating that risk factors for poor HRQoL and psychological distress are being female, lower educational attainment, unemployment, unmarried status and a lack of stable financial circumstances and low household income (less than $20 000 per annum). Other reviews on cancer where SCT patients are included indicates that a subset of individuals face severe difficulties as adults regarding the socio-economic situation that are due to cognitive-, emotional- and health problems (53-55). Research has been mainly carried out in population studies on the

relations between socio-economic factors and HRQoL (56, 57). Much points towards the fact that HRQoL varies depending on the person's socio-economic group. This is also the case when disease is a controlled variable-HRQoL is lower among the poorly educated and working class than among civil servants (56). Single unemployed women generally have a lower HRQoL than men: a higher income, higher education and socio-economic group are associated with better HRQoL. Apart from the fact that HRQoL has been shown to decrease with rising age (in studies in an age span from 20 and above shows that after 60 it decreases considerably), and women in particular consider themselves to have lower HRQoL than men mainly due to depression and pains. It is especially noteworthy that is the group of younger women who have problems with depression (56).

HRQoL and clinical research – clinical relevance

In the beginning of the 1990s the number of new QoL instruments increased dramatically in scientific literature which resulted in the clinicians becoming more familiar with the QoL concept and including it in clinical trials (7). HRQoL studies should exist to find new information of clinical value and for the development of health care and there is a "health paradox" that makes it meaningful to measure HRQoL in the field of medicine (20). In other words, an improved state of health appraised from a disease-specific assessment is not automatically connected to an increase in well-being or that the individual herself experiences an improvement in health. Highlighting areas that are problematic and where the patient herself experiences low HRQoL makes it possible to concentrate allocations on both preventative and follow-up care and psycho-social support for these "risk areas".

However the issue is still topical of how to translate HRQoL studies into clinical work. There is a lack of clear guidelines for how we will be able to use and interpret the data the patients themselves give us about their HRQoL (58, 59). This results in a situation where there are still very few interventions in health care based on HRQoL outcomes from the patients (60). Naturally this can be explained due to certain obstacles to taking measurements and using HRQoL in the clinics, such as a lack of time. Another explanation is also that there are shortcomings in understanding and interpreting the results, e.g. what a change in the scores implies or the reason for differences in scores between groups (58, 61).

Measuring HRQoL in children and adults

There is a difference in how children and adults perceive the causes of disease and treatment, which results in a challenge in order to ask the right questions concerning HRQoL (7). What adults value as significant quality of life factors can be different from what children and young people experience as important, this applies to everything from the functional level (physical/social activities) to social relationships (3, 62). The interpretation of the questions in a HRQoL instrument can be influenced by which development phase the child is in, and that in turn influences the outcome (4). The evaluation of the child's own HRQoL is also changed while passing through these development phases, especially when the child grows older and is confronted with changes/expectations in external life (63, 64). The change in state of health and the stress of being exposed to a life-threatening disease can result in the patient adapting herself in a new way to the environment, and even changes her inner values regarding what is important to her quality of life (response shift) (47). Spieth & Harris (12) described the different HRQoL areas for children as follows (which apply to adults to some degree);

State of illness: Physical symptoms are the most accepted variable for measuring health status and are interpreted sometimes as actually measuring HRQoL. But even if the child has some symptoms of disease it does not necessarily influence HRQoL negatively and result in difficulties in adjusting - the so-called “health paradox”.

Functional status: often characterized as the ability the child has to participate in carrying out different age-related activities. This area includes taking care of oneself, agility, physical activity, role playing e.g. play and leisure activities. The concept of functional status is dependent on HRQoL even if there is a clear distinction between the two. From a medical professional assessment angle, functional status is the degree to which the disease/treatment affects the patient, while HRQoL also includes and focuses on the subjective evaluation of this effect (1).

Social functioning: the area covers the individual’s ability to maintain social relationships, number/or quality of relationships. Children’s social functioning is mainly related to friends of the same age, but also how one relates to family, teachers and health professionals. Research has shown that chronically ill children do not differ very much from healthy children when it comes to social adaptation. A number of other areas for children and youth have been identified, e.g. for cancer patients. Questions of appearance are important when specific functional impairments do arise, such as for instance Alopecia (the patient loses hair), short stature etc (65).

Who is to evaluate?

A proxy is the person who answers and evaluates HRQoL for the patient, instead of the patient making her own evaluation. One example of a proxy, in the case of children and young people, can be a parent, health professional or teacher etc. For an adult patient, a proxy estimation is made by a relative or a health professional. Studies on children where the validity of the proxy's answers is examined indicate that the parents mostly answer in the same way in relation to other "proxies", as compared to when the patient/child answers (66). Often the proxies underestimate the patient's symptoms, QoL and mental health, regardless of who is the proxy (66). This means that the child can have a higher experienced HRQoL despite a functional impairment. On the other hand, the child's own estimation of her health state corresponds better with the doctor's estimation than with the parent's (67). Because the child lives in a family structure, these relationships are very much affected, and the parent often acts among other things as a "gatekeeper" for the child's health (23). Research has shown a strong link between the parent's availability to give care and the child's health and well-being (23). There are some areas of HRQoL where there is a larger correspondence between children's and parent's estimations (68). The physical areas of HRQoL have shown to have a high correspondence (68). However, there is a worse correspondence regarding the emotional and social (functions of) HRQoL. Previous research also indicates that parents have more difficulties estimating their child's internalized problems such as worry and depression, than externalized difficulties like acting out and aggression (69). There is also a higher correspondence in estimated HRQoL between parents and chronically sick children than parents with healthy children, but no direct connections between age and gender (68). Although, the chosen instrument for the study, the disease of the child and the state of mental health in the parents can have some influence on proxy-reported HRQoL (70). For example in a study concerning children with asthma the results showed that while taking measurements on very small children, it worked very well with a proxy (70). But with older children starting from primary school, the correspondence between child and parent/proxy diminishes and the child's own estimation of HRQoL becomes more important. Children who estimated a low HRQoL also had a parent that was depressed (68). Parents that estimated a lower HRQoL for their children were shown to be more influenced by stress disorders and also experienced that their child was more sensitive (69). If the parent has a more

supportive focus which implies them thinking more about what can be achieved and having more perseverance, i.e. looking more for opportunities, the result is that both the parents and children estimate a higher HRQoL (71). This can be contrasted with a lower estimated HRQoL, when the parent has a more protective attitude that presupposes them thinking about safety and responsibility basing their view on the danger and problems of the situation (71).

STEM CELL TRANSPLANTATION

Historical background

Allogeneic stem cell transplantation (SCT) or as it was previously called allogeneic bone marrow transplantation (BMT) has been performed since 1975 (72) at Karolinska University Hospital, in Huddinge (previously known as Huddinge Hospital) which was the first to perform SCT in Sweden on children and adults. The first trials with BMT in humans were performed in the 1950s (73). Transfusing bone marrow from donors to patients resulted in the growth of blood cell-producing bone marrow and mature donor cells in peripheral blood which showed that there was a chance of curing leukemia, bone marrow failure and immune system defects using this method. However problems with the graft-versus-host disease (GvHD) which could not be brought under control initially made the widespread use of SCT more difficult. GvHD is an immunological reaction where the transplanted T lymphocytes from the donor create an opposite rejection reaction attacking the patient's organs. After the HLA systems (human tissue types) were described at the end of the 1960s, successful transplants could be carried out from HLA identical siblings. During the 1970s the techniques were refined and improved, and the control of infections and GvHD improved in SCT which led to the method being used more and more. The first SCT in Huddinge Hospital on children was performed in 1978. Of the more than 3200 adults and children from the whole country who have had SCT so far (2008), 450 children under 16 years of age have been through the treatment at Karolinska University Hospital. At present around 50 children per year are transplanted in Sweden allogeneically and almost half of the transplants take place in Karolinska Huddinge.

Stem cells-Allogeneic SCT

The hematopoietic stem cells in the bone marrow provide a continuous production of all blood cells including the different types of leukocytes, the platelets and the red blood cells throughout the whole lifespan. In the first years of life, bone marrow is present within all skeletal bone cavities, but as we grow older the amount of functional bone marrow decreases. The hematopoietic stem cells can be collected (stem cell harvest) from either the peripheral blood after stimulation with granulocyte colony stimulating factor or directly from the bone marrow. In allogeneic SCT the patient receives stem cells from another healthy individual (donor) and therefore receives completely new hematopoietic and immune defense systems. In patients with malignant disorders, the adopted immune system can help to fight any remaining cancer cells, the so-called Graft-versus-Leukemia/Tumor effect (GvL/T). This effect is closely related to the presence of GvHD. A central aspect to balance these risks and benefits is to get a donor with a HLA-type as compatible as possible.

The SCT procedure

Immediately before the SCT itself, the patient is given a preparative regimen including chemotherapy and/or irradiation. Many of the defense systems that normally protect the human body from infection are temporarily disabled during the procedure (73). During the first weeks following transplant the patient is essentially aplastic with absent or low levels of white blood cells and platelets, and may also suffer from mucositis. This leads to a high risk of life-threatening infections and hemorrhages and the patient often requires continuous blood transfusions and systemic antibiotics (73). Chemotherapy, immuno-suppression and mucositis often cause nausea, diarrhea, and anorexia with the need for intravenous parenteral nutrition. Skin reactions, and renal and hepatic dysfunctions are also frequent (65). The child is protected in reverse isolation with a parent staying in the room, until the transplanted stem cells have engrafted and the leukocyte counts are increasing.

Related /Unrelated Donors

Allogeneic SCT presumes that the patient receives fresh bone marrow/stem cells from a related or unrelated donor. The so-called HLA antigens occur on all nucleated cells in the human body, and according to Mendelian law the chance of two siblings having identical HLA is 1:4. The likelihood of finding an HLA-identical unrelated donor is statistically small but has been greatly facilitated by large registries of volunteer donors.

In the worldwide cooperation on marrow donors since the 1990s, SCT with an unrelated donor has increased and at present more than around two thirds of children receive transplants from related/unrelated donors at Karolinska University Hospital, Huddinge (74).

Indications for SCT

The predominant diagnoses treated with SCT are malignant blood illnesses such as acute or chronic leukemia; otherwise they are non-malignant illnesses such as severe aplastic anaemia, certain inherited metabolic diseases such as severe immune deficiencies and haemoglobinopathies. To highlight the most commonly treated cancer diagnosis, i.e. acute lymphoblastic leukemia which affects about 80 children in Sweden each year - about 78 % will at present be cured with conventional chemotherapy (75) (NOPHO ALL 2000 protocol). When conventional curative strategies fail due to poor response to therapy or relapse into disease, stem cell transplantation can offer a curative potential, although the indications for treatment with SCT have changed over the last few decades (76). The increased availability of alternative donor sources, new diagnostic criteria, particularly in leukemia disorders, and the stage of the disease and the perceived prognosis under given circumstances and not only on the diagnosis are important today when referring a patient for SCT. Consequently, SCT is only carried out when other forms of treatment are judged to be of no use. The follow-up care entails the child coming for annual check-ups; this can change and happen less frequently when the child transits to meeting adult oncologists. Contact with a medical social worker has been added to the long-term follow-up for the last five years.

Results of the Treatment and Survival

Several aspects affect the treatment results after SCT. One important aspect is the patients' original diagnosis and the severity of the disease i.e. the stage of the disease the patient is at when the transplant takes place (77). Another important factor is the compatibility between the donor's stem cells and the receiving patient (77). Allogeneic SCTs have a higher risk of life-threatening medical side effects than autologous SCT, because of the donor compatibility issue and the risk of acute GvHD (65). However, in leukemia there is a greater risk of relapse after autologous SCT compared to allogeneic SCT. Today most children who are in immediate need of allogeneic stem cell transplantation (SCT) can be offered this treatment in developed countries. The chances of surviving SCT have also improved. Children who undergo stem cell transplantation

are more adversely affected by its side effects because they are at a more sensitive stage of biological, psychological and cognitive development. Treatment before SCT and conditioning regimens may vary - one of the factors being whether or not the child has a malignant condition. The decision on whether to accept an unrelated donor is also influenced by the severity and prognosis of the disease, because unrelated grafts have been associated with more complications and lower survival (12). One potential risk is also secondary cancer in later life, although this risk is seldom manifested during childhood, but is latent for decades following SCT (78). For diagnoses such as ALL, the cumulative risk of solid tumors after transplant was reported to be 11 % after 15 years (79). The predominant secondary malignancies in children are tumors of the brain and thyroid, in children who were under the age of 5 at SCT and who received irradiation (79). The mortality due to treatment is 15 % although it is lower in non-malignant diseases than in malignant diseases. With leukemia the relapse mortality is approximately 30 % (78, 80).

Late effects

The 60%-70% of children who make up the group of longterm SCT survivors often have a number of late effects to contend with (80). Late effects following allogeneic SCT are consequences firstly due to the patients' original disease and treatment, and secondly due to toxicity associated with the conditioning regimens of SCT treatment. The late complications of SCT are considerably greater than those associated with more conventional forms of cancer treatment, particularly in growing and pre-pubertal children (65, 81).

The follow-up medication to prevent or treat (toxic effects of antibiotics, antifungals or immuno-suppressive medication) infections or GvHD also adds to the strains on the patient. GvHD is the most serious problem after SCT. In the case of chronic GvHD, which appears more than three months after the transplantation, there are skin and mucous membrane changes, the liver and intestinal tract are affected, the appetite is diminished. Sometimes GvHD results in reduced movement in the joints and diminished functioning of the lungs. Besides chronic GvHD there are often late effects that affect the endocrine organs (e.g. affected pubertal development), heat and lungs, kidney function and CNS. Cognitive problems can be especially pronounced in children who have undergone full body irradiation at a young age (81, 82). Generally, most longterm survivors suffer some late effects, but only a minority sustain very severe late effects (83, 84). The use of total body irradiation, in particular, is known to

cause sterility, cataracts, cognitive problems and impaired growth. Common infections which are normally not dangerous, can be critical for a child with reduced immune defenses and e.g. lead to pneumonia (77). After SCT the patient/child is very sensitive to infections (especially for the first three months) and should avoid large gatherings of people and not go to school for at least six months afterwards.

Previous research into HRQoL – SCT

SCT is an aggressive form of theraphy that generally entails major strains on both the children and their families throughout all the stages of treatment (61). The long hospital stay and resultant isolation can affect both the child's and the whole family's HRQoL (67, 85, 86). The child becomes more dependent on its parents, does not go to school, or to any age-related activities or engage in social relationships for several months. When a family member (most often a sibling) is the donor for the child there can be certain strains on the functioning and relationships within the family (87). HRQoL researchers have also pointed out the importance of discriminating between the different malignant diseases as the treatment situations and the long-term consequences vary, e.g. between children with solid tumors and leukaemia. (88, 89). These include both somatic and psychological effects that impact on the lives of these families (86) (87). Syrjala's[i] (90) recent overview of OoL studies on SCT patients, mainly adults, she found that they generally rate their QoL as high, although certain problem areas could be identified. Syrjala also observed that not much was known about QoL, particularly in a longer perspective, among children after SCT. In 1994, Andrykowski (84) noted that it was adults who had been the focus of post-SCT QoL research and that increased attention should be devoted to QoL after pediatric SCT. This observation still remains true (61) . The successful development of SCT and also increased availability of donor sources combined with improved supportive care, means that long-term survivors today have the opportunity to live relatively normal lives for many years (91, 92). There is an agreement that surviving childhood cancer and SCT does not create any serious psychological or social problems for the majority of patients. However, there is an important subset of patients (15-30 %) who experience ongoing difficulties (93). Regarding cognitive functioning in children post-SCT, studies have shown mixed results where some indicate significant developmental delays (25, 82), and others demonstrate general normal development (54, 94). Pre-transplantation self-reported physical and mental health are more strongly associated with HRQoL after SCT than commonly noted baseline clinical predictors, such as age and disease risk (95).

Previous research indicates that problems in terms of body image can lead to lower quality of life (96). There is a risk for these children to have growth impairments following earlier treatment and/or SCT. Short stature has sometimes been considered to cause lower HRQoL (97), although other studies do not confirm this (98). Being below the age of 3 at the time of SCT has been mentioned as a risk factor for developing psychosocial difficulties, since this group generally suffers greater cognitive impairment (82). Cognitive, academic and psychosocial functioning in long-term *adult* survivors following SCT in childhood are areas that have been highlighted in previous studies (54, 93, 99). A majority of adults following SCT in childhood experience problems with fitness, pain, fear and emotional stress (100). In recent years, it has been emphasized that it is important not only to consider the risk factors in the lives of these children and adolescents, but also to remember the importance of protective factors, such as family cohesion, which promotes resilience to stress (101). A longitudinal study presenting pre- to post-transplant data indicated high psychosocial vulnerability before SCT in patients (102, 103). Family cohesion and the child's behavioral ability to adapt are strongly related to post-SCT HRQoL (104). Psychosocial factors in children and parents before SCT affect the parents' distress after treatment (102). In addition, many parents are also well aware of the risk of a secondary cancer in their child because of radiation (86, 103).

AIMS OF THE STUDY

The main purpose of this study was to gain increased knowledge of the life situation, the quality of life and health in long-term survivors following pediatric allogeneic SCT. The focus in this study is on health-related quality of life to be used to develop care and follow-up care from a long-term perspective. All the data is compared to reference data, either norm- or other chronically-ill comparison groups. This was approached with the following specific aims:

Specific aims

To evaluate HRQoL and late effects from the perspective of long-term surviving children and adolescents surviving at least 3 years after allogeneic stem cell transplantation.

To evaluate HRQoL from a parental perspective in SCT children and adolescents and to compare these findings with the patients' own evaluations.

To identify risk factors as well as protective factors affecting HRQoL and to identify patient groups and parents with specific needs of support.

To evaluate HRQoL in adult survivors, following paediatric allogeneic SCT.

To describe the socio-economic and psychosocial situation in adults following paediatric SCT by comparing the findings with national register data and population studies.

METHODS

The study presented in this thesis is subdivided into five parts describing HRQoL, health and the socio-economic situation in long-term survivors of pediatric allogeneic SCT. Three of the five studies concern the views of SCT children and adolescence and their parents, and the other two studies pertain to long-term survivors who have reached adulthood. The study designs of the Studies I-V are cross-sectional, descriptive, correlational and comparative.

SAMPLES

Papers I-V are based on three samples: SCT children[1] and their parents, and adults post-pediatric SCT. Children with severe neuro-degenerative disorders that were manifest prior to SCT were not included.

Papers I-III. Children (n=54) aged nine years or older, at least three years since SCT and who visited the Karolinska University Hospital, Huddinge for their yearly post-transplant follow-up, were asked with their parent/parents to participate in the study (Table X). These patients underwent SCT during from 1983 to 2000. The time elapsed since allogeneic SCT was 3-20 years (mean= 8). We chose the nine year age limit to ascertain that the participants would be able to respond to the instruments independently. The parents (n=42), who accompanied their children, also participated in the study on the same occasion. Two children/families declined to take part. Leukemia and MDS were the dominant indications for SCT, accounting for a total of 59.6%. Recipients, of a related donor or unrelated graft were n=32 versus n=19. Thirty-three children in the study group received total body irradiation in pre-conditioning. In Papers II-III all patients n=42 who were accompanied by their parent (n=42) were included.

[1] For simplicity the terms "children" are used to designate the whole age range up to adulthood. The definition of "child" in the study group in this thesis is due to the fact that the patient still attends the "Children's Clinical Department " at the Karolinska University Hospital, Huddinge. The patient takes a decision at the age of 16 years to be transferred to the adult oncology department or stay for a few years more in the children's department.

Papers IV-V. All adult patients (age >19) surviving for at least five years after having undergone SCT as children (age at SCT, range 1–16 years; median =10 years) between 1978 and 2001 at the Karolinska University Hospital, Huddinge, Sweden, and who had moved from the Children's Department to the Adult Hematology Service, were asked to take part. Forty five percent of the adults (n=73) had been transplanted as children between 1991-2001. Out of these 73 patients, ten were lost for follow-up purposes or were living abroad, six persons declined to take part in the study while four did not complete the study questionnaire (Table 1). There were no significant differences between participants and non-participants regarding demographic and disease characteristics (Table 1). Two patients with severe neuro-degenerative disorders that were manifest before SCT were not included in the study. A total of fifty-three persons took part (73%) and received a questionnaire to be returned to the center. The majority of diagnoses were malignant e.g ALL, AML, chronic myeloid leukaemia (CML), myelodysplastic syndrome (MDS) and other patients had non-malignant diagnoses such as severe aplastic anaemia, thalassaemia major, various metabolic disorders, heamophagocytic lymphohistiocytosis (HLH) or severe combined immunodeficiency (SCID).

Table 1. Patient Characteristics of participating and non-participating adult SCT survivors **(Papers IV-V)**

	Participants N (%)	mean (s.d.; median; range)	Non-participants N (%)	mean (s.d.; median; range)
Total number of SCT patients	53 (73 %)		20 (27%)	
Age at time of study (years)		26 (5.8; 24; 18-42)		28 (6.4; 26; 20-42)
Age at SCT (years)		10 (4.4; 10; 1-16)		10 (4.3; 10; 2-16)
Age 1–5 Age 6–12 Age 13–16	11 (21 %) **24 (45 %)** **18 (34 %)**		4 (20 %) 9 (45 %) 7 (35 %)	
YEARS SINCE SCT		16 (6.4;17; 5-28)		17 (5.1; 18;9-26)
Gender Female Male	 23 (43 %) 30 (57 %)		 9 (45 %) 11(55 %)	
INDICATIONS FOR SCT Malignant disorders Nonmalignant disorders	 35 (67%) 18 (33%)		 15 (75 %) 5 (25 %)	
Donor graft Unrelated Sibling, Parent,	 6 45 2			 1 16 2
Total body irradiation yes/no	 33(62%)/ 20(38 %)			 15(75%)/5(25%)

Comparison groups

For group comparisons in relation to a general population in Papers I-III, the participants were compared to other populations from studies reported elsewhere. In Papers I-III as comparison groups for SCHQ-CF87, we used the study group from Norrby's (personal communication) report (105) on Swedish children with JIA (Juvenile Inflammatory Arthritis), as well as the US norm values (22). For parent proxy-report (SCHQ-PF50) we used a large reference US population (22) For ITIA and SOC, we used the study and control groups from Räty (106) who investigated 158 adolescents with uncomplicated epilepsy in the 13-22 age group, comparing their QoL with a random sample of 282 Swedish adolescents in the same age group and residential areas. For the youngest children in the SCT group we used norm group values for the instruments (27, 107).

For comparison in Papers IV-V, a large Swedish national Swed-Qual reference group of adults collected in 1998 was used (108). From this group an age-matched random sample consisting of 357 individuals (age 19-42 years, mean=27 years) was extracted (Brorsson B, personal communication, (108)). Other populations used as comparison groups have been reported elsewhere; HAD (37), SOC-13 (109). In Paper V as a norm for socio-economic comparisons, data from Statistics Sweden (110) from 2005 describes two age ranges; 20-24 years (n= 2163) and 25-44 years (n= 5156) were used.

INSTRUMENTS

Swedish version of Child Health Questionnaire (SCHQ-87/SCHQ-50) The Swedish version of the Child Health Questionnaire (SCHQ) is a generic instrument designed to measure in parallel both the parent's and the child's perceptions of child health and well-being of several areas in life (22, 105). It does so by means of separate proxy reports (SCHQ-PF50) and child self-reports (SCHQ-CF87). The questionnaire focuses on the child's psychosocial and physical functioning and was originally developed for children aged 5-18 (22). SCHQ-CF87 has 87 questions for children about the following health factors (HRQoL dimensions): physical functions, general health appraisal, changes in health, limitations in school work and activities with friends due to emotional and behavioral difficulties, mental health, general behavior and self confidence, functioning in the family/family cohesion.

The proxy form, SCHQ-PF50, is an adapted version of the North American cross-cultural, self-administered instrument consisting of 14 concepts that can be summarized into two summary component scales representing physical and psychosocial health. The child form, SCHQ-CF87, is analogous to SCHQ-PF50 and is identical to it as regards 12 of the components while the scales known as Parental impact – Time and Parental impact – Emotional are omitted and there are no physical or psychosocial summary scales. Individualized scale scores are normalized to a range from 0 (worst) to 100 (best). A higher score reflects better perceived QoL. Both the parental and the children's forms have been validated in several countries (111-114), including Sweden (105). The scales used in SCHQ-PF50 (parent form) and SCHQ-CF87 (child form) also have good internal consistency with a reported Cronbach's Alpha ranging from .86-.94. In Papers I-III, Cronbach's Alpha ranged from .75-.91 for the children's form. The subscales used in SCHQ-CF87 met or exceeded the minimum standard for group level analysis (.70) and the values are comparable to those obtained from a US normal sample (n= 263, .63-.89)(22).

SWED-QUAL SWED-QUAL consists of 68 items with response formats of a Likert-type and the response scores are transformed into a 0-100 index(28). All scales are analyzed separately, not as one score for the total instrument. Paper IV includes 11 multi-item and two single-item scales which concern different aspects of health-related quality of life such as the physical, mental and social domains. The patient is asked to reflect on the weeks immediately prior to the questionnaire. A higher score indicates better functioning and well-being. In Paper IV the Cronbach's Alpha coefficient of the multi-item scales ranged from 0.78 to 0.97. In Paper V the scale "Cognitive Functioning" was used separately.
Questions on self-image (2 items), infertility (3 items), sexuality (1 item) and whether the subjects had received information and advice on sexual matters were added to the questionnaire.

HAD Hospital Anxiety and Depression scale (HAD) is a self-assessment scale for detecting depression and anxiety in patients (35-37). It is also a reliable and valid instrument for measuring the severity of an emotional disorder (37). HAD consists of 14 items each with 4 answer alternatives: 0 (no problems) to 3 (very severe problems). It has 2 subscales, one for anxiety (seven items) and one for depression (seven items). A score sum of 8 to 10 indicates severer problems, and greater than 11

indicates possible clinical case (37, 39, 109). In Papers IV-V the Cronbach's Alpha coefficient was 0.85 for the anxiety scale and 0.87 for the depression scale.

Sense of Coherence (SOC-13) Antonovsky (48) introduced "Sense of Coherence" (SOC), a measure of a global tendency to view life situations as comprehensible, manageable and meaningful. In adults a high SOC has been shown to work as a stress moderator SOC (sense of coherence) has been developed to measure an approach to life which, according to empirical research, can increase resistance in case of stress and therefore be a health-promoting property (115). In all the papers SOC-13 was used, it is an abbreviated variant that has proved reliable (115). In adults, a high SOC score has been proved to work as a stress moderator. The role of SOC in child and adolescent health has remained largely unexplored, although there are some studies that show that SOC has a stress-moderating effect in adolescents (116). Another version of SOC, " How do I feel? ", for children under the age of 10 (107) was used in Study I. According to Antonovsky (48), the original "Sense of Coherence" scale (SOC) has good internal consistency, with a reported Cronbach's Alpha greater than .70. Räty (106) also found SOC-13 to be adequate, with a reported Cronbach's Alpha of .83 for the total score. In Studies I-III, Cronbach's Alpha was .87. In Studies (IV-V) the Cronbach's Alpha coefficient was 0.91.

I think I am (ITIA) (27), is a Swedish instrument frequently used in both research settings (25, 26) and clinical contexts in Sweden, in mainly psychological studies. ITIA is a self-report scale standardized on a sample of Swedish children and is intended for use in assessing self-esteem in children and adolescents (27). The scale includes descriptions of a child's conceptions of himself/herself. There are two versions, one for children aged 7-10, and another for the age group 11-16. It measures the following five factors: (i) physical components, (ii) skills, (iii) psychological well-being, (iv) relationships with parents and family, and (v) relationships with others. Each factor uses the same number of statements, randomly organized. Each statement has four alternatives for adolescents and two for children. Positive correlations have been demonstrated between ITIA scores on the one hand and mental health and peer popularity on the other (27). Validity and reliability as measured by internal consistency have been shown to be adequate. Cronbach's Alpha on the total score ranged from .71-.82 for the 11-16 version of ITIA (27). In Papers I-II, it was .88 for the total score, and ranging from .63-.84 for the subscales.

Subjective Health and Symptom Inventory Checklist A Subjective Health and Symptom Inventory Checklist was developed by J Winiarski and U Forinder with the help of statistical expertise, at the Children's Hospital, Karolinska University Hospital Huddinge and is based on clinical experience specifically relevant for SCT-patients, The instrument has been tested, contains check questions and has good internal consistency.

CHILDREN *Papers I-III*: A self-assessment checklist was designed, including 29 items, subdivided in four blocks (Symptom/Body Pain/Activity/School). All of the items are not included in the four subdivisions as some of them were not included as they were categorical**.** Thirteen of the items requested the patient or his parents to grade the severity and /or the frequency of symptoms or problems on a scale of 0-3. A higher value indicated better health. The mean score of the items in each block was calculated. The activity block asked about e.g. the level of participation in physical exercise in and out of school and for fatigability. The school block asked for cognitive problems, school aptitude and mobbing. The pain block contained items on pain and a VAS scale, while the subjective symptom block contained items on e.g. GvHD- and late effects-related symptoms and problems such as dryness of skin, mucous membranes and eyes, alopecia, nausea, GI tract problems, disturbed sleep, etc. Cronbach`s alpha coefficient for internal consistency was 0.90.

ADULTS *Papers IV-V*: Some of the items above were excluded to be used in the adult SCT population (physical activity in and out of school, school aptitude and bullying). Items were subdivided into four blocks (symptom frequency/problem level symptoms/ Body pain/ cognition). The items requested patients to grade the severity and/or frequency of symptoms or problems on a scale of 0-3, with higher scores indicating better health. The mean score for the items in each scale was calculated. The pain scale included items relating to pain levels, while the subjective symptom scale included items, relating to GvHD and late effects, such as dryness of skin, mucous membranes and eyes; alopecia; nausea; gastro-intestinal problems; sleep disturbances, etc. The cognition scale concerned concentration and memory problems. The Cronbach's Alpha coefficient for the scales ranged from 0.70 to 0.92.

The Lansky and Karnofsky functional scales The Karnofsky Performance Index was designed to measure the self-rated level of patient activity and medical care requirements. The Karnofsky Performance Index (117) was used for the age group of

16 years or above. The psychosocial status is not taken into account. It is a frequently-used instrument in QoL investigations among adults. The similar Lansky scale (118) for children below age 16 is a proxy-rated instrument based on the level of play activity. Like the Karnofsky Index, it is a docile score offering ten responses ranging from 10 (moribund) through 100 (normal function)**.** A pediatrician assessed the scores in consultation with the patient or family.

Medical records-Late effects score A physician blinded to the outcome of the HRQoL studies reviewed each patient's medical records and assessed any reported late effects. But, also information about the original diagnosis, secondary cancers, cytostatic medication and whether patients had received total body irradiation or not. In Paper I-III the presence of late effects in each of eight problem categories was assessed by an experienced physician (JW) on a scale of 0 (no symptoms) to 3 (uncontrolled or debilitating disease). The following eight categories were defined: neurological symptoms, cognitive function according to the level of supportive measures needed in school and psychologist's reports, chronic graft-versus-host disease (GvHD), pulmonary function based on symptoms and spirometry, growth impairment according to growth charts, problems involving appearance and alopecia, skeletal pain/osteonecrosis and renal dysfunction. Infertility and cataracts were not included in the rating. A total late effects score was calculated for each patient as the sum of the eight category scores. A higher late effects score thus reflected more numerous and severe late effects.

In Paper IV-V we classified late effects according to the NCI Common Terminology Criteria for Adverse Events v3.0 (119). Late effects were assessed in each of twelve categories on a scale of 0–4 (0=no symptoms, 1=minor symptoms, 2=moderate symptoms, 3= severe, 4=debilitating or life threatening disease). An individual's total late effects score was calculated as the sum of the twelve category scores. The number (n) and percentage of SCT adults (%) at each of five total scores levels are described, where a total score of 4–10 represents either several or more severe sequelae. N/A not applicable; Growth impairment has a maximum score of 2. Score 1 = stature ≤-2 SD, according to norm.

Socio-economic information the information about socio-economic factors was collected by means of a standard self-assessment questionnaire used in a national study; Living Conditions Survey (ULF) (http://www.scb.se/LE0101-EN) (110), such

as level of education, occupation and personal finances. The issues addressed and the definitions used in Paper V are as follows: *Education*/*Employment/ /Student /Labor market programs /Disability pension /Long-term sick leave/Lack of cash margin/savings: /Difficulty in managing day-to-day expenses/financial crisis /Equivalence/equivalent disposable income/average income/Social ties*. Information about members' annual taxable income was obtained from the tax authorities (120).

Table 2. Overview of the instruments used in Papers I-V

	Paper I	Paper II	Paper III	Paper IV	Paper V
SCHQ-CF 87 (22)	X	X	X		
SCHQ-PF 50 (22)		X	X		
I Think I Am (27)	X				
Children's SOC (107)	X				
SOC-13 (48)	X	X	X	X	X
Subjective Health and Symptom Inventory Checklist	X	X	X	X	X
SWED-QUAL (28)				X	X
HAD (36)				X	X
Socio-economic questions (110)					X
Lansky/Karnofsky functional scales (117, 118)	X	X	X	X	

PROCEDURES

Ethical considerations - patient consent Approval for all studies was obtained from the Human Research Ethics Committee of the Karolinska Institutet. The studies were performed at the Karolinska Universitetssjukhuset, Huddinge. An ethical consideration in the study was to offer further psychosocial support to those adults post-paediatric SCT who were in need and asked for this.

In Papers I-III patients and their parents were informed about the study by letter well ahead of their visits. The subjective health and symptom inventory checklist was also sent to them for completion at home prior to their visit. During the visit both the patient and parents (when present) were given information together, and the parents were then asked to sit in another room so as to avoid situations in which patients and

parents influenced each other. The symptom checklist was sent out with the notification of the check-up and asked for it to be completed at home and left in the ward at the visit. Each patient had a special time set aside for filling in the forms. This was done in a room outside the outpatient ward. The patient and parents (when they were present) were given information together and then the parents were asked to sit in another room so that parents and patients would not influence each other. That procedure was agreed to in all cases. Both parts also generally agreed with the statement that parents and patients had different opinions on these matters. The research leader stayed with the patients in order to be on hand to assist if necessary. One and a half hours was set aside for the whole procedure. The main research leader (UF) was present in 75% of the cases. Three more research leaders, all experienced in meeting children and adolescents with severe illnesses, helped in the study. The Lansky and Karnofsky scores were assessed by a pediatrician in consultation with the patient or family.

In Paper IV-V all the adults who had had been through allogeneic stem cell transplantation as children at the Karolinska University Hospital, Huddinge were asked (all diagnoses were included). The patients were informed in good time about taking part in the study. Information was sent by letter to the patients. The questionnaire regarding HRQoL and health was sent out by post and this was followed up with a reminder phone call. The clinical data was compiled from the patient's medical records.

Data analysis

The statistical methods used in Papers I-V are presented in Table 2. All the statistical methods used in Papers I-V are listed. Various analyses were conducted in the papers summarized in this thesis. Descriptive statistics were used and numbers and percentages are presented to describe the distribution of patients and characteristics in each study. Cronbachs Alpha coefficients is used for all instruments because most of the instruments are not used on populations such as SCT children or adults post-pediatric SCT. The data in Papers I-V was analyzed using the Statistical Package for Social Sciences (SPSS version 12.0/14.0/16.0 for Windows). The statistical methods applied in the different papers are described below. Significance at $p < 0.05$ is assumed throughout.

Table 2. Overview of statistical methods used in Papers I-V

	Paper I	Paper II	Paper III	Paper IV	Paper V
Students T-test	X	X			
Mann-Whitney		X	X	X	X
Pearson product moment correlation coefficient	X	X	X	X	X
Standard multiple regression			X		
ANOVA				X	
Chi 2			X	X	X
Cronbach's Alpha	X	X	X	X	X

Papers, in detail regarding each study's statistics (I-V)

Paper I

Unpaired T-test analysis was performed to explore any statistically significant differences between the study group (the SCT group) and the historical comparison groups (22, 105-107), as well as to investigate gender and age-related differences. Construct validity was assessed by correlating SCHQ and ITIA with the SOC-13 health instrument using the Pearson product moment correlation coefficient. Intercorrelations between health variables on the one hand (late effects and subjective health and symptom inventory checklist) and the two QoL variables on the other hand were also investigated, as was the correlation between age at the time of SCT and all instruments used in the study. Cronbach's Alpha was used to determine the internal consistency of the instruments.

Paper II

Paired Students T-test analysis was performed to explore differences in judging HRQoL and health between parents and children in the SCT group. The HRQoL scores from SCT parent group and US parent norm group (22) were compared using the Students T-test. The Pearson product moment correlation coefficient was used to assess inter-correlations between SCHQ-PF50 and health factors measured in children

(Subjective symptom inventory/Late effects score/Lansky-Karnofsky scales). Cronbach's Alpha was used to determine the internal consistency of the instruments. Non-parametric statistics were applied when splitting data according to age group on the SCHQ PF50-scales and years post-SCT, because most of the scales were not normally distributed. Differences between these groups were tested with the Mann-Whitney U-Test.

Paper III

Categorical data are presented as percentages. The mean (and range) of values is given for continuous data. All the results (SCHQ parent/child form, Lansky and Karnofsky functional scale, SOC 13) were analyzed in categories with children diagnosed with malignant disorders or non-malignant disorders, related or unrelated donor and TBI or no TBI. HRQoL scores from the SCHQ child/parent form and health forms (Lansky-Karnofsky functional scale, SOC 13) were not normally distributed, so non-parametric analyses were performed using the Mann-Whitney U-test and Chi-square statistics. Relationships between variables were also investigated by correlating the SCHQ parent/child form subscale scores with donor (related/unrelated), total late effects score and subjective health and symptom inventory checklist, using the Pearson product moment correlation coefficient. Standard multiple regression analysis was made separately for the dependent HRQoL variables of the Physical and Psychosocial Summary scales (SCHQ-PF50). The independent variables after SCT included diagnosis (leukemia / non-malignant), donor (unrelated / related), TBI or no TBI and the total late-effects score.

Paper IV

Descriptive statistics, the Student's T-test, and the non-parametric Mann-Whitney U-test were used to assess the effects of age, diagnosis, donor, treatment, subjective and objective health on HRQoL domains in the SWED-QUAL and HAD Scale. One-way analysis of variance was performed to explore differences in scores between the adults post-pediatric SCT and a comparison group (28, 108). The Pearson product moment correlation coefficient was used to assess construct validity by correlating SWED-QUAL and SOC-13 with HAD. Intercorrelations between health variables and the HRQoL instrument and SOC and HAD were also examined.

Paper V

Descriptive data are presented in percentages to illustrate socio-economic factors such as education, occupation, financial circumstances and social ties. The circumstances of the SCT-group are compared with those of a normal population (Statistics Sweden, www.scb.se/LE0101-EN) by computing expected values for the SCT group according to the distribution of sex and age. Test of differences were made by an χ^2-test (categorical variables) or one sample T-test (continuous variables). For the comparisons of cognitive function, a healthy gender- and age-matched national norm group (personal communication B. Brorsson) was used (108). The non-parametric Mann-Whitney U-test was used to assess the effects of gender and age on psychological ill health (anxiety, depression and cognitive functioning).

Statistical consideration

Two problems in the statistical analyses ought to be notified. In the first hand a number of statistical tests are performed, increasing the risk of getting significant results by change (type 1 error). On the other hand the groups used in this the test are small in number leading to low or moderate power- the possibility to detect differences (type II error). These problems are handled by taking more notice on the pattern of test outfalls and results than concentrating on outfalls of single tests.

SUMMARY OF RESULTS

In this section summarizing the results of paper I-V I expressions as "good", "better"/"higher", "worse"/"lower" imply statistically significant results. The statistical details are given in each paper, respectively.

PAPER I

Forinder U, Lof C, Winiarski J, Wl. Quality of life and health in children following allogeneic SCT. *Bone Marrow Transplantation* 2005; **36**(2)**:** 171-176.

This paper focuses on the children's point of view. The main questions asked in paper I are how the children evaluate their own HRQOL, and the relationship to the subjective/objective health in this group of long term surviving children following SCT. Comparisons were made with norm data (22) and data from other chronically ill children (105).

HRQOL

HRQOL scoring (SCHQ-CF87) differed significantly between children post SCT and comparison groups in several areas. As a group the SCT children had good self reported HRQOL and even better than norm in one area, general behaviour (BE). Children post SCT were below norm in the areas of bodily pain ($p<0.05$), general health and self-esteem ($p<0.01$). When compared to other chronically ill children, the study group had a better self-evaluated HRQoL than Norrby's chronically ill group (juvenile chronic arthritis) in the area "social role due to physical difficulties" (RP), but experienced worse general health (GH). The study group showed a trend that higher age correlated with a lower HRQOL in one area. Age at the time of the study correlated negatively with self esteem (SE) ($P<0.05$). Neither gender nor primary disease (malignant/nonmalignant disorders) had effect on reported HRQOL.

Subjective health

Most children were subjectively in good health although problems with pain were common in the study group, 44% of the group had troubles with pain. Three children reported having considerable difficulties at school. Lansky or Karnofsky function levels were at a median of 90, showing that the children following SCT had moderately good

physical functioning. Sense of coherence, using SOC 13, was normal and on a par with comparison norm group.

When correlating self evaluated HRQoL (SCHQ-CF87) and children's subjective health the results revealed that fewer symptoms were associated with better self esteem (SE)($P<0.05$), mental health (MH)($P<0.01$) and also with more participation in physical activities ($P<0.01$). Mental health in this group was also affected when the child reported more problems with pain or with aspects of school.

Objective health

When conducting a medical record-based scoring of late effects it was revealed that 25 percent (n=13) of the children post-SCT had moderate to severe late effects. Short stature was the most prevalent late effect. Cognitive problems were noted in 11 children but were not a hindrance to school attendance (including special-needs school), social activities. GvHD-related symptoms were found in 7 children after 3-9 years post-SCT. Two children had a previous history of severe osteonecrosis with skeletal pains, which had required using a wheelchair and orthopedic surgery. Alopecia (hair loss) and dermal symptoms (severe skin problems) due to GvHD was found in eight children following SCT. No association was found between the physician-rated late effects and HRQoL. But children with severe GvHD perceived their general health as inferior. Children who had objective cognitive problems perceived a worse psychosocial HRQoL in some areas compared to the SCT group as whole. These areas were regarding limitations in their social role due to emotional and behavioral difficulties (RE/RB), but also general behavior (BE). No association was found between the physician-rated late effects and HRQoL. But children with severe GvHD perceived their general health as worse. Children who had objective cognitive problems perceived a worse psychosocial HRQoL in some areas compared to the SCT group as whole. These areas were regarding limitations in their social role due to emotional and behavioural difficulties (RE/RB), but also general behaviuor (BE).

PAPER II

Forinder U, Lof C, Winiarski J, Xd. Quality of life following allogeneic stem cell transplantation, comparing parents' and children's perspective. *Pediatric Transplantation* 2006; **10**(4)**:** 491-496.

The focus of this paper is the HRQoL in children following SCT from a parental perspective, and in comparison to the child's view. It also discusses how the parents' views are affected by the child's subjective self-assessed health situation and by the impact of the child's objective health i.e. physician-rated late effects.

SCT child's HRQoL assessed by parent

Parents of SCT children tended to evaluate a lower HRQoL for their child than the children themselves did. Although the scores of the different areas in SCHQ followed each other, the parent rated lower HRQoL in the areas of "social role due to physical limitation" (RP) ($P<0.01$) and "self- esteem" (SE) ($P<0.01$). "Self-esteem" was a HRQoL area which the SCT children already reported as inferior than norm population in Paper I. "Bodily pain" (BP) was an area in which both parents and children scored a low HRQoL. When study group parents were compared to a normative group of parents of children without any chronic disease (22), the study group of parents evaluated a lower HRQoL for their children in both the psychosocial and physical areas. When looking at the specific areas (SCHQ-PF50), the SCT parents evaluated a lower HRQoL for their children in both the psychosocial and physical areas ($P<0.001$). Parents evaluated a lower HRQoL in eight out of 12 areas compared to norm group (22). The parents' emotional situation was also more affected by the child's condition than in the norm population (PE)($P<0.001$).

Parental perspective of HRQoL versus child's health

There was an association between SCT child's level of functioning and health and parents' evaluation of HRQoL (SCHQ-PF50). More severe late effects were associated with parents rating lower HRQoL in both the psychosocial and physical areas. The child's self-assessed subjective symptoms also had an association with the HRQoL rated by parents. Lower subjective symptom levels, less pain and fewer problems in school were associated with better psychosocial HRQoL. ($P<0.01$-0.05). A low score

for subjective symptoms was associated with a higher rated HRQoL in the physical area ($P<0.05$). High Lansky functional levels in younger children corresponded to a higher level of HRQoL rated by parents ($P<0.05$). In children 16 years or older a high Karnofsky score correlated with HRQoL in the physical area ($P<0.01$).

PAPER III

Lof CM, Forinder U, Winiarski J, Id. Risk factors for lower health-related QoL after allogeneic stem cell transplantation in children. *Pediatric Transplantation* 2007; **11**(2)**:** 145-151.

This paper explores whether possible risk factors such as diagnosis, donor choice and total body irradiation affect HRQoL. Considering both SCT children's and parents' HRQoL evaluation of the child, there is also a discussion about how physician-rated late effects and subjective health interact with HRQoL. Another question asked in Paper III is whether there was a group of children and parents with specific needs of support within the SCT group?

Children's diagnosis, health and HRQoL

Children with leukaemia assume their situation to be more problematic in the psychosocial area, with "limitations of role and social behavior due to emotional difficulties", than children with a non-malignant diagnosis. Children with leukemia also had more severe late effects ($p<0.05$). Seventeen percent of the children diagnosed with leukemia showed more serious problems with late effects, compared to 5 % in the non-malignant group. There was an association between severe late effects in the group of children with leukemia, and a low subjective health in the "activity" area.

Parents´ HRQoL rating

Parents of children with leukemia evaluated lower HRQoL for their children than parents of children with a non-malignant diagnosis did; this concerned both psychosocial and physical areas. If the child has leukemia, the parents also rate themselves as more negatively affected by the child's situation.. There is a negative association between four parent-rated areas in the leukemia group and more late effects, physical functioning, general health, self-esteem and "problems emotionally in their social role due to physical difficulties".

Donor, TBI, medical late effects and HRQoL

The psychosocial HRQoL areas were more affected in children who received a donor graft from an unrelated donor than in those receiving a sibling graft. Here children's and parents' points of view agreed. The type of donor did not affect the SCT children's subjective symptom ratings. Exposure to TBI or not did not correlate to any impairments of HRQoL, SOC or to the severity level of late effects. However, when conducting a multiple regression analysis it was only late effects that remained as the independent factor that contributed to a low HRQoL in the psychosocial and physical areas, as evaluated by parents ($P<0.001$-0.01).

PAPER IV

Löf CM, Winiarski J, Giesecke A, Ljungman P and Forinder U. Health- related quality of life in adult survivors after pediatric allo-SCT. *Bone Marrow Transplantation* 2009; **43**,461-468.

This paper explores health status, HRQoL and late effects, and possible interactions between these aspects, in adult long-term survivors (n=53) after SCT in childhood.

HRQoL

To conclude, in this paper none of the following: age at time of SCT, late effect scoring of organ system function, TBI or original diagnosis (malignant/non-malignant) had any effect on self-reported HRQoL. However, the adults had a poorer HRQoL (SWED-QUAL) than norm (108) in 9 out of 13 areas. The largest clinically relevant effects and poorer HRQoL areas were predominantly general health perceptions, cognitive functioning, partner relations and sexual function. Increasing age at the time of study was associated with a better HRQoL in the areas of emotional well-being ($P<0.01$), physical health ($P<0.01$), relationships ($P<0.05$) and cognition ($P<0.05$). Time post-SCT was also associated with better self-rated HRQoL in these areas. However many of the adults had mental and emotional problems. Thirty five percent had problems on a possibly clinical level from anxiety and depression (HAD), and this group also had poorer HRQoL and sense of coherence (SOC).

Self-assessed health status and physician-rated late effects

A majority of the adults were subjectively and objectively in good health. Twenty-four percent had objectively severe problems from medical late effects. Moreover, 53 % of

the study-group reported problems with bodily pain. Forty-two percent of the study group also self-reported considerable problems with memory and concentration. This was insufficiently documented in the medical records, reporting cognitive problems in only 9 % of the patients. Many of the adults (55%) responded that they are infertile and expressed difficulties with this. The mean heights and weights were below norm, especially for post-SCT men.

Interaction between subjective, objective health and HRQoL

In line with SCT children in Papers I & III, there was a strong association between self-rated symptoms and HRQoL in most areas in the adult group ($P<0.01$).

Severe physician-rated late effects indicated more reported difficulties in the areas of physical functioning, emotional well-being and satisfaction with close relationships.

PAPER V

Löf CM, Winiarski J, Ljungman P, Forinder U. The socioeconomic and psychosocial circumstances of adult, long-term survivors of allogeneic stem cell transplantation in childhood or adolescence. *(Manuscript)*

The focus in Paper V was to describe the present social circumstances, such as education, employment, financial circumstances, social ties and psychological functioning, in adult survivors (n=53) after SCT in childhood. These aspects were compared to a reference group from the Swedish national population registry. Another question asked in this study was whether there was any association between psychological ill health, cognitive dysfunction and present socio-economic circumstances in the study group.

Socioeconomic circumstances

The group of long-term surviving adults had a lower level of education and a poorer establishment on the labor market (15 % were unemployed, 13 % were in receipt of a disability pension or long-term sick leave) than the national population. Delayed family formation also seemed to be a problem in adult SCT survivors compared to the norm, 56 % were single in the ages 25-42 with 81 % among the younger members.

Regarding economic resources, no difference could be found between the study group at large and the norm population. However as regards age, gender and financial circumstances, this study revealed that younger subjects and women have more

difficulties with limited economic resources and problems with managing day-to-day expenses.

Psychological ill-health

In Paper IV it was revealed that 35 % had clinical problems with anxiety and depression, and this paper (V) showed that together with cognitive difficulties these problems were most common among the younger adults (aged 19-24 years) in the study group. No significant relationship could be found between socio-economic circumstances and psychological ill-health. However, those adults who had clinical anxiety and depression experienced more cognitive difficulties with concentration, memory and cognitive vitality.

DISCUSSION

QUALITY OF LIFE AND HEALTH AFTER ALLOGENEIC STEM CELL TRANSPLANTATION DURING CHILDHOOD

This study was performed in order to gain increased knowledge about the living conditions of the children who had been through SCT. The primary focus was to shed light on the child's own perspective, with the emphasis being put on health and quality of life several years after the transplantation. The secondary focus was to shed light on HRQoL and the socio-economic situation for the long-term surviving children who have reached adult age. A large proportion of previous HRQoL research on children is based on proxy assessments (1) and not on the child's self report, and there is little focus on the very late outcomes for the children following SCT who have reached adulthood (90, 121, 122).

Children's HRQoL and proxy reports

In spite of life-threatening illness and trying treatment, the children themselves felt they had good HRQoL 3-19 years post-SCT, both when we compared them with other children from norm populations or children with other chronic conditions. This is in line with earlier HRQoL studies (85, 90, 93, 123) after pediatric SCT, and it is also confirmed by recent research (61, 124, 125). The focus in this study is not on the parents of children following SCT, rather they are included as "proxies" for their children. We notified that, after complementing with proxy assessments of the children's HRQoL and health, there were a number of deviations between the children and their "proxies".

A central finding was that the parent proxies report a less favourable HRQoL for the child, compared to the child's self report of HRQoL. Moreover, the parents HRQoL scores are better correlated to the medical record derived late effects scores than children's own assessment of their HRQoL. It was clear that many of the parents had a more pessimistic view of their child's HRQoL a long time after the SCT. This discrepancy has previously been brought to light being dependent on several aspects (67-69,87,101, 126-127) the scale of the child's illness influence (i.e. treatment period/degree of difficulties), but also the parents' psychosocial situation and mental state. The parent's view of their child's life situation and HRQoL is also colored by worries about uncertainty about the child's future (86). The study parents were

themselves negatively emotionally affected, and felt anxiety about their child's situation and health. This became most clear when the child endured serious late effects and when the child had a malignant diagnosis (61). Another explanation for the parent's perspective can be the imminent risk of a relapse; in malignant cases i. e. leukaemia, it is 30 % (80, 86). This is something that may be less obvious for the child when we enquire into HRQoL (68, 128).

One possible interpretation of the difference is that the child's answers may not be as influenced by anxiety about the future as their parents. Children can also be assumed to perceive their HRQoL as relatively good after SCT, because they have a more "here and now/in the moment" thinking. Children and adolescents might be more prone to repress or deny the reality of their health situation (or both) (128). This is important to take into account in the clinical interpretation of the results. Another factor to keep in mind is the parents' protective and caring role that can bring empowerment to the child's experience of their situation and HRQoL (101, 104). This can explain why "our" children feel they have a rather good situation in spite of several health problems following SCT. But also, these results reinforce earlier research that one has to be clear who evaluates the child's HRQoL (61, 68). Todays research has ventured far past the stage of "if children can speak for themselves and at which age" regarding measurements of HRQoL in groups with children. We now appreciate that both the children's and the caregiver's perspectives are important (129). A more important question is; which is the best way to obtain the information and detect important differences between the children and their caregiver that need to be considered clinically. These aspects also became very evident in this study. To conclude, clarity with regard to who is responsible for assessing the child's HRQoL is crucial when interpreting paediatric HRQoL studies.

Adults post-pediatric SCT

There is a growing number of adults who underwent SCT as children and the side effects can affect them more adversely because of their young age at transplant, and thus their more sensitive stage of biological, psychological and cognitive development at SCT (65, 82, 97). We had in mind the children's situation after SCT when we interpreted the results of the adults treated with SCT in childhood (Papers IV and V). What happened then? At that point in time previous research has dealt with health and the psychosocial situation of children at the most a few years after the treatment of

children who had undergone SCT (61, 122). The adult long-term survivors, who were transplanted as children 5-28 years ago, apparently had a poorer reported quality of life in several areas than the transplanted children had stated, albeit at a much younger age (Papers I-III). Although there are some inherent differences between the HRQoL areas investigated in children and the now adults, the adult group evaluated their HRQoL as poorer in most areas, both when it came to physical health and the psychosocial situation. The most prominent HRQoL problem areas in adults were mental health difficulties with anxiety/depression, cognitive problems with concentration and memory, with social relationships and sexuality issues.

Health and disease impact

HRQoL/QoL is a holistic concept and the intention was to research and describe how life is working out for the children as SCT recipients at a particular point in life is and not just to find out about the impact of the disease on their lives (4, 7). The concept of disease impact and QoL are different concepts and they need to be distinguished from each other (4). This research has a general theoretical approach to HRQoL instead of a more disease-based perspective (4). Health aspects are labeled and measured separately, but used as correlates, which on the other hand led to the study also investigating the long-term surviving children's situation from a "disease impact" perspective.

In the wake of the SCT a large proportion of the children (44 %) and of the adult group (53%) in our study stated that they had trouble with physical pain. The physician- rated health was relatively good in around 75% of the patients with few or no obvious complications from late effects. On the other hand, around 25% of the groups, in both the children's study and the adult study; suffer from several late effects. However, it is important to emphasize that the SCT children's subjective experience of health had stronger associations with a low HRQoL than the objectively-rated health. This is also in agreement with previous research (104). The findings from Papers II-III with parents' reports confirm that more severe medical late effects following SCT affect the family (103). But importantly the parents' proxy rated HRQoL tends to be more positive in the physical area if the child reports fewer symptoms, less pain and also fewer problems in school. It also became clear that medical late effects had a limited impact of affecting self-reported HRQoL in the adult group post-pediatric SCT (Paper IV), compared to the subjective health and many self-rated symptoms. This was in line

with the results from the studies with SCT children (Papers I-III). One main finding in this thesis is the fact that self-rated health has a greater impact on how the patients experience their own health situation no matter if you are a SCT child or adult. This supports the notion that the subjective perception of health is of specific importance to HRQoL (122). Self-rated health is an important "risk indicator" and has shown to produce more predictive information than the traditional clinical measurements (45, 46). This also emphasizes the fact that the PRO of symptoms and health is very important in follow-up care (6, 130).

Age and HRQoL

The age at which the study was carried out seemed to be relevant for how the persons in question experienced their life situation both in childhood (children's study) and for the children who had reached adulthood. We noticed that the older children had lower self esteem than the younger children following SCT, although self esteem was lower in children than the norm population in general. This can be a consequence of the cognitive development of the child at different ages, which leads to the child thinking differently about him/herself and of his/her situation (131). We also noticed that age affected how the adults (post-ped SCT) assessed their HRQoL. With increased age and the length of time that had elapsed since SCT, there was a better rated HRQoL in the areas that had been "problem areas" (cognitive, relationships, physical health). Another positive aspect was that SCT at a young age (<3 years) did not have any effect on the self-reported HRQoL. that thus was not obviously affected by any assumed or real cognitive problems in the very young age group, problems which may have negative effects on psychosocial life (82). This was the case both for the children and the adult (post-ped SCT) group. However, the number of very young children at SCT in the study was rather low (n=17) making these observations less certain. We observed that the five children who had the most severe medically-assessed cognitive problems had more difficulties in psychosocial HRQoL areas than the others. This was also noted in the adult group with a high share of self-reported cognitive difficulties.

In addition to the observation that the children can have problems continuing into adulthood, it is also an indication that HRQoL is rated differently during the various developmental phases of life (4, 61, 131). The HRQoL can also be affected in the young SCT patient facing new challenges/expectations in the world outside, in the various transition phases, which may lead to a re-evaluation of HRQoL during life

(response shift) (47). In QoL shifts, the emphasis on certain "areas" which are important at one time is shifted into new areas of importance. Such inherent fickleness perhaps contributes to the difficulties in defining the concept and to work with HRQoL issues starting from a theoretical model (4, 6).

For example, with age - appearance and physical health take on different expressions or become more important (100, 132, 133). The adults (post-ped SCT) in the study did not have any noticeable problems with their appearance when we asked the questions. Problems related to appearance are a factor that can result in an inferior well-being and more anxiety for the long term survivor (134). However, body height and weight are affected in adults following paediatric SCT, and are relatively below the norm. This was especially apparent for the men in the adult study group. There were also a number of physical difficulties in this group. Sexuality and fertility are e.g. part of becoming an adult and our group of adults reported problems in this area, and were of the opinion that they had not received enough support and advice on these issues. The shortcomings in this aspect do not seem unusual. A recent review (135) with SCT adults showed that, according to the SCT patients themselves, there was a continuing lack of information and discussion about the problems with sexuality and infertility, which became apparent and persisted long after treatment.

Socio-economic situation

When exploring other psychosocial and socio-economic aspects of life, adults post-pediatric SCT experienced several problematic areas that were highlighted in comparison with age-matched population-based studies (110). These results indicate that the transition from childhood/adolescence to adulthood can be even more challenging for the SCT group, especially regarding cognitive and psychosocial functioning (54, 93, 99). This has also been noted in previous research with adults treated for cancer in childhood (53, 55). SCT is a most aggressive treatment that often follows a difficult and demanding treatment period. Psychologically and physically, becoming a young adult is a challenging time and even more challenging if you are faced with impaired health that has ensued since getting a life-threatening disease and having a long period of treatment in childhood. An important finding to consider in the adult group was the high incidence of self-reported cognitive impairments and psychological ill-health, and the correlation to a lower level of education, a less favourable financial situation and a lower employment rate. Attention should also be focused on the discord between the commonly self-reported

cognitive problems and the apparently underreported cognitive difficulties in the patients' medical journals. In a review about long-term surviving adult SCT patients it was found that many patients also suffered from memory problems as well as several severe psychological ailments (136). The conclusion however was that, psychological problems such as loneliness and existential distress after having a life-threatening illness and going through a tough treatment such as SCT entails, can be just that and does not imply that one is a clinical "case"(39).

However, the adults in the present study that have severe problems from anxiety, depression or cognitive deficiencies also have a much worse situation than the rest of the group. Another main finding was that the most affected socio-economically were the young people and women in the study group, although this pattern is in line with national register data and population-based studies (110) (SCB). Moreover, adults post-pediatric SCT generally have a disadvantaged situation in comparison with age-matched national register data. Again it is important to point out that the results show a trend where HRQoL improves with age in the areas which were otherwise problematic e.g. cognitive issues, relationships, and physical health. This can be interpreted that in the transition to becoming an adult, the young individual has not yet found strategies to handle the new challenges they are faced with, but which she/he will later learn to deal with (131). Or the fact that later in adult life an adaptation to the "status quo" may have taken place, a reassessment of HRQoL which leads to learning to live with the difficulties (47, 59).

Recent studies

During this research a few more articles of HRQoL after pediatric SCT have appeared. A recent review (61), concerning HRQoL in survivors of BMT for paediatric malignancy, presented among previous research- results from studies that have been published from 2005 to 2008 (129, 138-140). HRQoL seems to improve for 4-12 months post-treatment, but during a pre-transplant period it is negatively compromised. Further it seemed that social and family functioning is crucial to the child's long-term HRQoL and should be empowered, but still, only few studies are about such family interventions (124). Clarke et al. (61) continue the earlier discussion that the change in HRQoL over time is an important aspect to investigate further into this group with long-term survivors after paediatric SCT, as medical and psychosocial late effects can occur further on in life. The studies of Barrera et al. (125, 140) shows that an

improvement in the child's social competence can occur around one year after SCT, but normalizes after two years back to how it was before SCT. For the SCT child - age, physical health status and depression were factors which influenced internalized/external behavior factors and social factors. The adolescents who underwent SCT had poorer HRQoL than the younger children (140). But according to the parent it was the occurrence of GvHD, the time since the SCT and the age of the parent (in this case the mother) that were relevant for the child's social competence and education. The mother reported improved school competence for her child, the older the child was at the time of SCT. Risk factors for inferior psychosocial situation and lower school aptitude were very young age at SCT, inferior physical health and also the distress level of the mother. The younger the mother and the greater the distress, the lower the school aptitude and social competence as well as more internalised/externalised problems in the child (125). Another observation is that the child-parent agreement was best during the most acute treatment phase, suggesting that the parent is a good proxy at this time (138). Our observations in adults are in line with what other studies (135) with SCT adults have shown, i.e. a subset of SCT long-term survivors experience persistent symptoms of anxiety and depression, problems regarding sexual issues and fertility concerns. Also that there is a majority who despite medical late effects which appeared earlier or later in life have a skill, a job or are studying (135).

Methodological discussion

Despite a relatively good HRQoL in general, the fact that the adults who underwent SCT during childhood have major problems that show up "between the lines", also reveals that it is very important to make use of a multi-dimensional approach in order to obtain this information. The novelty of this study is first; to describe the children's situation from their own view. Secondly it is a comprehensive description of the current life situation of adult patients that are no longer affected by the immediate post-SCT problems but are challenged by various problems in different stages in life. A rather drastic interpretation might be that the parents' more pessimistic picture of HRQoL and of the possible dangers in the future for their child to some extent came true when we investigated the situation of the now adult previously pediatric patients (Papers IV-V). Again, it is important to point out that it is a limited subset or "risk group" of the total study group, including adults and children, who have more obvious difficulties. A majority of the adults do live a normal life. The fact that there is a minority who are

more affected by more severe problems, as a consequence of the illness and the treatment, is supported by other studies (61, 123). However, the interpretation is limited by the study design. The study is cross sectional and not longitudinal. The life situation for children being transplanted more recently or today (e.g.the children in this study) may present another picture when they become adults, than we see today in the adult group transplanted 1-2 decades ago. Another limitation might be that the study group of children and adults is limited in size, but it is from one single center with a very long experience of paediatric SCT and includes consecutive non-selected cases. Despite these difficulties, one should feel encouraged by the overall positive outcome and the favourable situation for a majority of transplanted children. SCT is a life-saving, but life-altering treatment as well and with a growing number of long-term surviving adults treated in childhood. These studies confirm the fact that young patients are saved to live a meaningful life, regardless of the many challenges.

This study of HRQoL and life situations has given us a broader and deeper insight in how their life situation evolves after treatment. As is discussed in the QoL/HRQoL research field, the various aspects of the wide concept of QoL, somehow need to be integrated, despite the psychometric difficulties. The present thesis confirms that it is meaningful to obtain such a comprehensive picture of their life situations (4).

On the other hand another aspect to consider regarding conceptual issues of using HRQoL is the question of how one's life can be separated into what is affected by a disease from that which is influenced by all one's current and past experiences. This is one possible explanation of the lack of theoretical models in several HRQoL instruments (4, 6). Another important question is whether the individual can make these distinctions /accurately when answering a HRQoL questionnaire. Yet, an ongoing discussion concerns the extent to which the causal factors influence the fact that HRQoL differs from individual to individual in a study group (7, 14). Personality is one such internal factor but there are also external factors such as e.g. socio-economic status. Another aspect that has been highlighted recently is what impact health- and life style behaviors can have on long-term survivors' overall wellbeing (137). What we cannot see in this study is e.g. how the family's situation was from the beginning. Family function and the socio-economic situation of the parents are likely to have an impact on the childs HRQoL. Socio-demographic aspects may also be considered i.e. where these patients live, with possible local opportunities or limitations. The socio-economic perspective was included when we investigated the adult study group.

CLINICAL IMPLICATIONS

In conclusion, pre-transplant predictors can be decisive for how children's HRQoL will be in the longer term following SCT, and depending whether the problem is detected and addressed in time. One approach is to survey the child's HRQoL, individual resources, family functioning and social skills in the initial pre-transplant stage as an integrated part of the comprehensive SCT-care program, and let it affect the planning of follow-up care. In recent years, it has been emphasized that it is not only important to consider the risk factors in the lives of these children and adolescents, but also to remember the importance of protective factors, such as family cohesion, which promotes resilience to stress. One important clinical task might thus be to monitor the group with severe problems and try to find ways of improving their situation.

The study also emphasizes that medical follow-up should be integrated with psychosocial support including advice in sexuality and fertility issues, particularly when patients enter adulthood. As in previous studies (82, 141) the need of neuropsychological evaluation and support is also evident. Through continuous and obligatory support these young people could be aided in developing and coping with their cognitive faculties, thereby improving their school aptitude and academic skills, as well as strengthening their position when seeking employment in the labour market. This thesis clearly envisages that a number of significant problems follow with the successful progress of SCT as a now established and lifesaving treatment in previously lethal paediatric disorders. The non-medical, i.e psychosocial problems need to be more actively addressed. These important issues should never be allowed to overshadow the positive outcomes of SCT and should thus constitute an urgent invitation towards the development of relevant supportive measures that will aid our patients to a better life situation and QoL after SCT.

SUMMARY AND CONCLUSIONS

As a group, children reported a good HRQoL as compared to norm and to other chronically ill children. Their HRQoL was related to the degree of self-rated symptoms, but did not correlate to the severity of physician-rated late effects.

Parent proxy HRQoL scores tended to be lower than children's own scores. The level of physician-rated late effects and the child's self-assessed symptoms were associated with a lower parental rating of the child's QoL. Clarity with regard to who is responsible for assessing the child's QoL is thus crucial, and so are complementing perspectives.

A lower HRQoL was found in SCT children with leukaemia, mainly related to a higher degree of late effects. Factors such as total body irradiation or an unrelated donor had limited or no impact.

Adult survivors after SCT in childhood perceived an overall good HRQOL and health, although severe psychological and cognitive problems are common. HRQoL improved with age and with time after SCT. A majority, however, was troubled by infertility and had not received sufficient advice in sexual matters.

Long-term adult survivors after paediatric SCT lead fairly normal lives, while a subgroup encounters difficulties with a lower educational level, psychological ill-health and a poorer financial situation, particularly among the younger and women.

A number of significant problems follow with the successful progress of SCT but these issues should not be allowed to overshadow the positive outcomes of SCT, rather they emphasize that medical follow-up should be integrated with psychosocial and neuropsychological support including advice in sexuality and fertility issues, when patients enter adulthood.

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who have contributed to this research, and especially to all those children with families and former peadiatric patients that participated in the study and shared their experiences.

Ulla Forinder , my wonderful principle supervisor for introducing me to the "quality of life" area, and guiding me through the world of science and methodology. Thank you for your "hands on" supervising, support and caring, both in work and in life. For also being a great "room-mate" and always having an ear open when I ask about something in the other side of the room, ready for peptalk or an interesting discussions.

Jacek Winiarski my co-supervisor who have been very supportive in the research process and encouraging during my period as a doctoral student. Thank you for sharing your deep knowledge as a medical professional and introducing me to the clinical situation of these children. And for all the interesting meetings and scientific discussions "around the round table" in your office.

Stig "Loffe" Elofsson thank you for sharing your knowledge in statistics and especially for all the practical help with the statistical analyses in the second half of this research.

Anders Gisecke for your industrious work with reviewing the patient's medical journals.

Per Ljungman for your invaluable contribution to the study with the adults.

Marianne Olsson head of the division of social work, Karolinska Institute, department of neurobiology, care science and society, for your support and important questions and suggestions for this research all the way through this journey, and to all my fellow doctoral students and collegues in the research group who have contributed during our fruitful meetings and discussions.

Ulla Norrby for sharing your knowledge about instruments and data in the beginning of this research.

Bengt Brorson, for generously sharing your reference group data on SWED-QUAL to our study with the adults.

Yvonne sjöblom, who I see as one of my academic mentors, **Patrick Karlsson** and **Lisa Sand** for your comments and helping me to bring clarity in the presentation of my research.

Ulf Lundberg Professor, Chess, Biological department at the Institution of Psychology Stockholm University for introducing me early on in my academic life to the multidisciplinary science of medicine and psychology.

Forinder family who have followed me through life and being supportive in an ”earlier life” before this research and in a way contributed.

Pernilla Lagergren for always being a step ahead and which inspired me to progress.

All my dear friends (no named and no one forgotten), Im so lucky to have you in my life! Thank you for all the fun and support, and **Celia** for giving me a “treat” from time to time at your Spa (Roslags Spa, Stockholm)

My parents, **Elisabeth and Kaj**, who inspired me to also have a positive attitude to life, and who always believe in me and support me even if you don’t always know what I am doing, and thanks mom for being a great grandmother and taking care of Leo, to my sister **Therese** (and Pong) with such an sunny aura around you and always something kind to say, you make my life brighter! To my brothers, **Johan** and **Thomas** and not the least my bonusfamily, **Hasse, Lisa** and **Manne**.

My mother-in-law, **Ann-Britt** for all the good food (deliverys) that has been strengthening, and to the rest of the **Miljateig family** for all the fun gatherings.

Magnus my fiancé for being supportive and interested during this journey, and to **Leo** our beautiful son and happy spirit who bring so much joy to life.

REFERENCES

1. Davis E, Waters E, Mackinnon A, Reddihough D, Graham HK, Mehmet-Radji O, et al. Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes. Developmental Medicine and Child Neurology. 2006 Apr;48(4):311-8.
2. Lindstrom B. QUALITY-OF-LIFE - A MODEL FOR EVALUATING HEALTH FOR ALL - CONCEPTUAL CONSIDERATIONS AND POLICY IMPLICATIONS. Sozial-Und Praventivmedizin. 1992;37(6):301-6.
3. Brülde B. Teorier om livskvalitet [Theories on quality of life]. Sweden, Lund: Studentlitteratur. 2003.
4. Wallander JL, Schmitt M, Koot HM. Quality of life measurement in children and adolescents: Issues, instruments, and applications. Journal of Clinical Psychology. 2001 Apr;57(4):571-85.
5. Bowling A. Measuring health-A review of quality of life measurement scales. 3 ed. Berkshire: Open University Press, 2005.
6. Lipscomb J, Snyder CF, Gotay CC. Cancer outcomes measurement - Through the lens of the medical outcomes trust framework. Quality of Life Research. 2007 Feb;16(1):143-64.
7. Fayers P, Hays R. Assessing quality of life in clinical trials- Methods and Practice. 2 ed. Oxford University Press. 2007.
8. Constitution of the World Health Organization. International Health Conference. New York, 1946.
9. Kuyken W, Orley J, Power M, Herrman H, Schofield H, Murphy B, et al. THE WORLD-HEALTH-ORGANIZATION QUALITY-OF-LIFE ASSESSMENT (WHOQOL) - POSITION PAPER FROM THE WORLD-HEALTH-ORGANIZATION. Social Science & Medicine. 1995 Nov;41(10):1403-9.
10. Eiser C, Vance YH, Seamark D. The development of a theoretically driven generic measure of quality of life for children aged 6-12 years: a preliminary report. Child Care Health Dev. 2000, 26: 445-456.
11. Nordenfeldt L. Samtal om hälsa: En dialog om hälsans natur. Stockholm: Liber/ Almqvist&Wiksell. 1996.
12. Spieth LE, Harris CV. Assessment of health-related quality of life in children and adolescents: An integrative review. Journal of Pediatric Psychology. 1996 Apr;21(2):175-93.
13. Wilson IB, Cleary PD. LINKING CLINICAL-VARIABLES WITH HEALTH-RELATED QUALITY-OF-LIFE - A CONCEPTUAL-MODEL OF PATIENT OUTCOMES. Jama-Journal of the American Medical Association. 1995 Jan;273(1):59-65.
14. De Civita M, Regier D, Alamgir AH, Anis AH, FitzGerald MJ, Marra CA. Evaluating health-related quality-of-life studies in paediatric populations - Some conceptual, methodological and developmental considerations and recent applications. Pharmacoeconomics. 2005;23(7):659-85.
15. Kaplan RM, Feeny D, Revicki DA. METHODS FOR ASSESSING RELATIVE IMPORTANCE IN PREFERENCE BASED OUTCOME MEASURES. Quality of Life Research. 1993 Dec;2(6):467-75.

16. Lindstrom B. Measuring and improving quality of life for children. In. Lindstrom B, Spencer NJ, editors. Social Pediatrics. Oxford: Oxford University Press. P 571-585. 1995.
17. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. THE EUROPEAN-ORGANIZATION-FOR-RESEARCH-AND-TREATMENT-OF-CANCER QLQ-C30 - A QUALITY-OF-LIFE INSTRUMENT FOR USE IN INTERNATIONAL CLINICAL-TRIALS IN ONCOLOGY. Journal of the National Cancer Institute. 1993 Mar;85(5):365-76.
18. Anderson RT, Aaronson NK, Bullinger M, McBee WL. A review of the progress towards developing health-related quality-of-life instruments for international clinical studies and outcomes research. Pharmacoeconomics. 1996 Oct;10(4):336-55.
19. Joyce C R B., O'Boyle, McGee H. Individual Quality of Life-Approaches to Conceptualisation and Assessment. Harwood academic publishers. Singapore 1999.
20. Sullivan M, Karlsson J, Taft C. How to assess quality of life in medicine: Rationale and methods. Progress in Obesity Research: 8. 1999:749-55.
21. World Health Organization. Measurment of Quality of Life in Children. Geneva: Division of Mental Health, 1993.
22. Landgraf J M, Ware J E. The CHQ Users Manual, 2nd printing, The Health Institute, New England Medical Center: Boston, 1996.
23. Landgraf JM, Abetz LN, Denardo BA, Tucker LB. CLINICAL VALIDITY OF THE CHILD HEALTH QUESTIONNAIRE-PARENT FORM (CHQ-PF) IN CHILDREN WITH JUVENILE RHEUMATOID-ARTHRITIS (JRA). Arthritis and Rheumatism. 1995 Sep;38(9):795-.
24. Speechley KN, Maunsell E, Desmeules M, Schanzer D, Landgraf JM, Feeny DH, et al., editors. Mutual concurrent validity of the Child Health Questionnaire and the Health Utilities Index: An exploratory analysis using survivors of childhood cancer1999.
25. Arvidson J, Larsson B, Lonnerholm G. A long-term follow-up study of psychosocial functioning after autologous bone marrow transplantation in childhood. Psycho-Oncology. 1999;8(2):123-34.
26. Von Essen L, Enskar K, Kreuger A, Larsson B, Sjoden PO. Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment. Acta Paediatrica. 2000 Feb; 89 (2):229-36.
27. Ouivinen-Biergerstam P. 'Jag tycker jag är" ['I think I am'] Manual. Psykologiförlaget, Stockholm, 1985
28. Brorsson B, Ifver J, Hays RD. THE SWEDISH HEALTH-RELATED QUALITY-OF-LIFE SURVEY (SWED-QUAL). Quality of Life Research. [Article]. 1993 Feb;2(1):33-45.
29. Stewart A, Ware J. Measuring functioning and well-being. Durham:Duke University Press, 1992.
30. Larsen J, Nordstrom G, Ljungman P, Gardulf A, Iq. Factors associated with poor general health after stem-cell transplantation. Supportive Care in Cancer. [Article]. 2007 Jul;15(7):849-57.
31. Lindqvist R, Carlsson M, Sjoden PO, Yl. Coping strategies and health-related quality of life among spouses of continuous ambulatory peritoneal dialysis, haemodialysis, and transplant patients. Journal of Advanced Nursing. 2000 Jun;31(6):1398-408.

32. Hagsten B, Svensson O, Gardulf A. Health-related quality of life and self-reported ability concerning ADL and IADL after hip fracture - A randomized trial. ACTA ORTHOPAEDICA. 2006 FEB 2006;77(1):114-9.
33. Eriksson L, Nordstrom G, Berglund T, Sandstrom E. The health-related quality of life in a Swedish sample of HIV-infected persons. JOURNAL OF ADVANCED NURSING. 2000 NOV 2000;32(5):1213-23.
34. Wandell P, Brorsson B. Assessing sexual functioning in patients with chronic disorders by using a generic health-related quality of life questionnaire. QUALITY OF LIFE RESEARCH. 2000 2000;9(10):1081-92.
35. Zigmond AS, Snaith RP, Qv. THE HOSPITAL ANXIETY AND DEPRESSION SCALE. Acta Psychiatrica Scandinavica. 1983;67(6):361-70.
36. Snaith RP, Zigmond AS, Aza. THE HOSPITAL ANXIETY AND DEPRESSION SCALE. British Medical Journal. 1986 Feb;292(6516):344-.
37. Herrmann C, Wh. International experiences with the hospital anxiety and depression scale - A review of validation data and clinical results. Journal of Psychosomatic Research. [Review]. 1997 Jan;42(1):17-41.
38. Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JCI, et al., editors. Psychological Status in Childhood Cancer Survivors: A Report From the Childhood Cancer Survivor Study2009.
39. Hjermstad MJ, Knobel H, Brinch L, Fayers PM, Loge JH, Holte H, et al. A prospective study of health-related quality of life, fatigue, anxiety and depression 3-5 years after stem cell transplantation. Bone Marrow Transplantation. [Article]. 2004 Aug;34(3):257-66.
40. Brülde B, Tengland P-A. Hälsa och sjukdom- en begreppslig utredning. Lund: Studentlitteratur. 2003.
41. Medin J, Alexanderson K. Begreppen Hälsa och hälsofrämjande-en litteraturstudie [Concept of Health and Health promoting- a reveiw of the litterature]. Lund:Studentlitteratur; 2000.
42. Hälsoindex för den svenska befolkningen [Healthindices for the swedish population]. Rapport från ett utvecklingsprojekt. Stockholm: Statistics Sweden; 1992.
43. Förrutsättningar för ett nationellt hälsoindex []. Regeringsuppdrag. Stockholm: Epidemiologiskt centrum, Socialstyrelsen; 2003.
44. Kaplan R, Anderson J P, Ake C. Gender differences in Quality-Adjusted Life Expactancy: Results from the National Health Interview Survey. Clinical Journal of Woman's Health, 2001; 1 (1): 191-198.
45. Idler EL, Benyamini Y. Self-rated health and mortality: A review of twenty-seven community studies. Journal of Health and Social Behavior. 1997 Mar;38(1):21-37.
46. Bjoerner J, Kristensen T, Orth-Gomér K et al. Selfrated health: A useful concept in research, prevention and clinical medicine. Stockholm: Forskningsrådsnämnden;1996.
47. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. Quality of Life Research. 2006 Nov;15(9):1533-50.
48. Antonovsky A. Uraveling the Mystery of Health. How people manage stress and stay well. San Francisco: Jossey-Bass; 1987.
49. Donnelly J W, Eburne N, Kittleson M. Mental Health-Dimensions of Self-Esteem & Emotinal Well-Being. Allyn & Bacon, 2001.

50. Forsell Y, Hansson A. Psykisk ohälsa och behandlingsbehov utifrån ett befolkningsperpektiv. Stockholm: Enheten för psykisk hälsa, Psykiatrisk epidemiologi, Samhällsmedicin, Stockholms läns landsting; 2001. Rapport 2001:2
51. Fayers P M. Hand D J. Causal variables, indicator variables and measurement scales: an example from quality of life. Journal of the Royal Statistical Society Series a-Statistics in Society. 2002, 165; 233-253.
52. Zeltzer LK, Lu Q, Leisenring W, Tsao JCI, Recklitis C, Armstrong G, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: A report from the Childhood Cancer Survivor Study. Cancer Epidemiology Biomarkers & Prevention. [Article]. 2008 Feb;17(2):435-46.
53. Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voute PA, De Haan RJ, et al. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho-Oncology. [Article]. 2003 Apr-May;12 (3):213-25.
54. Phipps S, Dunavant M, Srivastava DK, Bowman L, Mulhern RK. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. Journal of Clinical Oncology. 2000;18 (5):1004-11.
55. Zebrack BJ, Chesler M, Tt. Health-related worries, self-image, and life outlooks of long-term survivors of childhood cancer. Health & Social Work. [Article]. 2001 Nov;26(4):245-56.
56. Burstrom K, Johannesson M, Diderichsen F. Health-related quality of life by disease and socio economic group in the general population in Sweden. Health Policy. 2001;55 (1):51-69.
57. Burstrom K, Johannesson M, Rehnberg C. Deteriorating health status in Stockholm 1998-2002: results from repeated population surveys using the EQ-5D. Quality of Life Research. 2007;16:1547-53.
58. Lee S J, Joffe S, Kim HT, Soice G, Gilman A L Wingard J R. Physicisians' attitudes about quality-of-life issues in hematopoetic stem cell transplantation. Blood 2004; 104: 2194-2200.
59. Sloan JA, Cella D, Frost M, Guyatt GH, Sprangers M, Symonds T, et al. Assessing the clinical significance of quality-of-life measures in oncology research: State of the science - Overview. Clinical Therapeutics. 2002;24:1-4.
60. Ayanian JZ, Chrischilles EA, Wallace RB, Fletcher RH, Fouad MN, Kiefe CI, et al. Understanding cancer treatment and outcomes: The Cancer Care Outcomes Research and Surveillance Consortium. Journal of Clinical Oncology. 2004;22(15):2992-6.
61. Clarke SA, Eiser C, Skinner R. Health-related quality of life in survivors of BMT for paediatric malignancy: a systematic review of the literature. Bone Marrow Transplantation. 2008 Jul;42(2):73-82.
62. Gerharz EW, Ravens-Sieberer U, Eiser C. Is quality of life measurable in children? Aktuelle Urologie. 1997;28(7):355-63.
63. Schultz KAP, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: A report from the childhood cancer survivor study. Journal of Clinical Oncology. 2007 Aug;25(24):3649-56.
64. Langeveld NE, Grootenhuis MA, Voute PA, Van Den Bos C, Tb. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psycho-Oncology. 2004 Dec;13(12):867-81.

65. Skinner R, Leiper A. Bone marrow transplantation. In: Wallace H, Green D (eds). Late effects of Childhood cancer. Arnold: London, 2004, pp304-320.
66. Sprangers MAG, Aaronson NK. THE ROLE OF HEALTH-CARE PROVIDERS AND SIGNIFICANT OTHERS IN EVALUATING THE QUALITY-OF-LIFE OF PATIENTS WITH CHRONIC DISEASE - A REVIEW. Journal of Clinical Epidemiology. 1992;45(7):743-60.
67. Parsons SK, Barlow SE, Levy SL, Supran SE, Kaplan SH. Health-related quality of life in pediatric bone marrow transplant survivors: According to whom? International Journal of Cancer. 1999:46-51.
68. Eiser C, Morse R, Ag. Can parents rate their child's health-related quality of life? Results of a systematic review. Quality of Life Research. [Review]. 2001;10(4):347-57.
69. Vance H, Morse C R, Jenney E, Eiser C. Issues in measuring quality of life in childhood cancer: measures, proxies and parental mental health. Journal of Child Psychology & Psychiatry. 200:42:661-667.
70. le Coq EM, Boeke AJP, Bezemer PD, Colland VT, van Eijk JTM. Which source should we use to measure quality of life in children with asthma: The children themselves or their parents? Quality of Life Research. 2000;9(6):625-36.
71. Eiser C, Eiser JR, Greco V. Surviving childhood cancer: Quality of life and parental regulatory focus. Personality and Social Psychology Bulletin. 2004 Feb;30 (2):123-33.
72. Gahrton G, Groth C, Lundgren G, Lockner D, Moller E, Sundelin P, et al. Bone marrow transplantation-an alternative treatment for aplastic anemia and leukemia. Lakartidningen , 1977: 74(2907-2911).
73. Thomas E D, Blume K G, Forman S J, Hematopoietic Stem Cell Transplantation. 2nd edition ed Blackwell Science, Inc., Malden, MA, USA, 1998.
74. Svenberg P, Remberger M, Svennilson J, Mattsson J, Leblanc K, Gustafsson B, et al. Allogenic stem cell transplantation for nonmalignant disorders using matched unrelated donors. Biology of Blood and Marrow Transplantation. 2004 Dec;10(12):877-82.
75. Gustafsson G, Kreuger A, Clausen N, Garwicz S, Kristinsson J, Lie SO, et al. Intensified treatment of acute childhood lymphoblastic leukaemia has improved prognosis, especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996. Acta Paediatrica. 1998 Nov;87(11):1151-61.
76. Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A, Icst; Ebmt J. EBMT activity survey 2004 and changes in disease indication over the past 15 years. Bone Marrow Transplantation. 2006 Jun;37(12):1069-85.
77. Gustafsson Jernberg A. Allogeneic stem cell transplantation in children-Identification and prevention of complications-Adoptive transfer of EBV-immunity. Thesis. Karolinska Institutet, Stockholm, Sweden, 2003.
78. Jernberg AG, Remberger M, Ringden O, Winiarski J. Risk factors in pediatric stem cell transplantation for leukemia. Pediatric Transplantation. 2004 Oct;8(5):464-74.
79. Socie G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. Journal of Clinical Oncology. 2000;18(2):348-57.

80. Gustafsson A, Remberger M, Winiarski J, Ringden O. Unrelated bone marrow transplantation in children: outcome and a comparison with sibling donor grafting. Bone Marrow Transplantation. 2000;25(10):1059-65.
81. Smedler AC, Winiarski J. Neuropsychological outcome in very young hematopoietic SCT recipients in relation to pretransplant conditioning. Bone Marrow Transplantation. 2008 Oct;42(8):515-22.
82. Smedler A C, Nilsson C, Bolme P. Total Body Irradiation: a neuropsychological risk factor in paediatric bone marrow transplant reciepients. Acta Pediatrica, 1995; 84: 325-330.
83. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. Journal of Clinical Oncology. 2005 Sep;23(27):6596-606.
84. Andrykowski MA, Greiner CB, Altmaier EM, Burish TG, Antin JH, Gingrich R, et al. QUALITY-OF-LIFE FOLLOWING BONE-MARROW TRANSPLANTATION - FINDINGS FROM A MULTICENTER STUDY. British Journal of Cancer. 1995 Jun;71(6):1322-9.
85. Phipps S, Barclay D. Psychosocial consequences of pediatric bone marrow transplantation. International Journal of Pediatric Hematology/Oncology. 1996;3(3):171-82.
86. Forinder U. I skuggan av cancer-benmärgstransplantation hos barn ur ett föräldraperspektiv[]. Phd Thesis. Department of Social work, Stockholm University, Sweden, 2000.
87. Kronenberger WG, Carter BD, Edwards J, Morrow C, Stewart J, Sender L. Psychological adjustment of mothers of children undergoing bone marrow transplantation: The role of stress, coping, and family factors. Childrens Health Care. 1998 Spr;27(2):77-95.
88. Boman K, Bodegard G. Long-term coping in childhood cancer survivors: influence of illness, treatment and demographic background factors. Acta Paediatrica. 2000;89(1):105-11.
89. Calaminus G, Weinspach S, Teske C, Gobel U. Quality of life in children and adolescents with cancer. Klinische Padiatrie. 2000;212(4):211-5.
90. Syrjala K. Assessment of Quality of Life in hematopoietic cell transplantation recipients. In: Blume K, Forman S, Appelbaum F (Eds) Thomas` Hematopoietic Cell Transplantation. Blackwell Science: Malden, 2004, pp 507-518.
91. Langeveld NE, Stam H, Grootenhuis MA, Last BF, Mq. Quality of life in young adult survivors of childhood cancer. Supportive Care in Cancer. [Review]. 2002 Nov;10(8):579-600.
92. Worel N, Biener D, Kalhs P, Mitterbauer M, Keil F, Schulenburg A, et al. Long-term outcome and quality of life of patients who are alive and in complete remission more than two years after allogeneic and syngeneic stem cell transplantation. Bone Marrow Transplantation. [Article]. 2002 Nov;30(9):619-26.
93. Kupst MJ, Penati B, Debban B, Camitta B, Pietryga D, Margolis D, et al. Cognitive and psychosocial functioning of pediatric hematopoietic stem cell transplant patients: A prospective longitudinal study. Bone Marrow Transplantation. [Article]. 2002 Nov;30(9):609-17.
94. Halberg FE, Kramer JH, Moore IM, Wara WM, Matthay KK, Ablin AR. PROPHYLACTIC CRANIAL IRRADIATION DOSE EFFECTS ON LATE COGNITIVE FUNCTION IN CHILDREN TREATED FOR ACUTE

LYMPHOBLASTIC-LEUKEMIA. International Journal of Radiation Oncology Biology Physics. 1992;22(1):13-6.
95. Andorsky DJ, Loberiza FR, Lee SJ, editors. Pre-transplantation physical and mental functioning is strongly associated with self-reported recovery from stem cell transplantation, 2006.
96. Madanswain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. ADOLESCENT CANCER SURVIVORS - PSYCHOSOCIAL AND FAMILIAL ADAPTATION. Psychosomatics. 1994 Sep-Oct;35(5):453-9.
97. Badell I, Igual L, Gomez P, Bureo E, Cubells J, Ortega JJ, et al. Quality of life in 87 pediatric patients after BMT. A study of the getmon. Bone Marrow Transplantation. [Meeting Abstract]. 1998 Mar;21:S218-S.
98. Sandberg DE, Voss LD. The psychosocial consequences of short stature: a review of the evidence. Best Practice & Research Clinical Endocrinology & Metabolism. 2002;16(3):449-63.
99. Ness KK, Bhatia S, Baker KS, Francisco L, Carter A, Forman SJ, et al. Performance limitations and participation restrictions among childhood cancer survivors treated with hematopoietic stem cell transplantation - The bone marrow transplant survivor study. Archives of Pediatrics & Adolescent Medicine. 2005;159(8):706-13.
100. Gruber U, Buchmann M, Kolb HJ, Hiddemann W, Vv. The long-term psychosocial effects of haematopoetic stem cell transplantation. European Journal of Cancer Care.. 2003 Sep;12(3):249-56.
101. Phipps S, Mulhern RK. FAMILY COHESION AND EXPRESSIVENESS PROMOTE RESILIENCE TO THE STRESS OF PEDIATRIC BONE-MARROW TRANSPLANT - A PRELIMINARY-REPORT. Journal of Developmental and Behavioral Pediatrics. 1995 Aug;16(4):257-63.
102. Phipps S, Dunavant M, Lensing S, Rai SN. Psychosocial predictors of distress in parents of children undergoing stem cell or bone marrow transplantation. Journal of Pediatric Psychology. 2005 Mar;30(2):139-53.
103. Fife BL, Huster GA, Cornetta KG, Kennedy VN, Akard LP, Broun ER. Longitudinal study of adaptation to the stress of bone marrow transplantation. Journal of Clinical Oncology. 2000;18(7):1539-49.
104. Barrera M, Pringle LAB, Sumbler K, Saunders F. Quality of life and behavioral adjustment after pediatric bone marrow transplantation. Bone Marrow Transplantation. 2000;26(4):427-35.
105. Norrby U, Nordholm L, Fasth A. Reliability and validity of the Swedish version of Child Health Questionnaire. Scandinavian Journal of Rheumatology. 2003;32(2):101-7.
106. Raty LKA, Larsson BMW, Soderfeldt BA. Health-related quality of life in youth: A comparison between adolescents and young adults with uncomplicated epilepsy and healthy controls. Journal of Adolescent Health. 2003;33(4):252-8.
107. Margalit M. Loneliness and coherence among preschool children with learning disabilities. Journal of Learning Disabilities. 1998;31(2):173-80.
108. Wandell P, Brorsson B, Aberg H. Quality of life among diabetic patients in Swedish primary health care and in the general population: Comparison between 1992 and 1995. QUALITY OF LIFE RESEARCH. 1998 DEC 1998;7(8):751-60.

109. Wettergren L, Bjorkholm M, Axdorph U, Langius-Eklof A. Determinants of health-related quality of life in long-term survivors of Hodgkin's lymphoma. QUALITY OF LIFE RESEARCH. 2004 OCT 2004;13(8):1369-79.
110. Statistics Sweden (Statistiska Centralbyrån) 2005. ULF (Living Conditions Survey) [www.scb.se/LE0101-EN]
111. Landgraf JM, Maunsell E, Speechley KN, Bullinger M, Campbell S, Abetz L, et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. Quality of Life Research. 1998 Jul;7(5):433-45.
112. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke R. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. Journal of Clinical Epidemiology. 2002 Jan;55(1):67-76.
113. Ruperto N Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology Clin Exp Rheumatol 2001; 19(4): S1-S9.
114. Selvaag AM, Ruperto N, Asplin L. The Norwegian Version of the Child Health Assessment Questionnaire and the Health Questionnaire, Clin Exp Rheumatol 2001; 19 (4 suppl 23): S116-120.115.
115. Eriksson M. UNRAVELLING THE MYSTERY OF SALUTOGENESIS- The evidence base of the salutogenic research as measured by Antonovsky's Sense of Coherence Scale. Folhälsan Research Centre, Health Promotion Research Programme. Åbo Akademis Tryckeri, Turku, 2007.
116. Torsheim T, Aaroe LE, Wold B. Sense of coherence and school-related stress as predictors of subjective health complaints in early adolescence: interactive, indirect or direct relationships? Social Science & Medicine. 2001 Sep;53(5):603-14.
117. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutics in cancer. In: MacLeod CM. (ed.) Evaluation of chemotherapeutic Agents. Columbia University Press: New York, 1949, 191-205.
118. Lansky SB, List MA, Lansky LL, Rittersterr C, Miller DR. THE MEASUREMENT OF PERFORMANCE IN CHILDHOOD-CANCER PATIENTS. Cancer. 1987 Oct;60(7):1651-6.
119. Common Terminology Criteria for Adverse Events v.30 (CTCAE). August 9,2006. http:ctep.cancer.gov/reporting/ctc_v30.htlm
120. www.skatteverket.se
121. Sanders JE, Syrjala KL, Hoffmeister PA, Foster LD, Wy. Quality of life (QOL) of adult survivors of childhood leukemia treated with chemotherapy (CT) or bone marrow transplant (BMT). Blood. [Meeting Abstract]. 2001 Nov;98(11):741A-2A.
122. Helder DI, Bakker B, de Heer P, van der Veen F, Vossen J, Wit JM, et al. Quality of life in adults following bone marrow transplantation during childhood. Bone Marrow Transplantation. [Article]. 2004 Feb;33(3):329-36.
123. Tsimicalis A, Stinson J, Stevens B. Quality of life of children following bone marrow transplantation: critical review of the research literature. European Journal of Oncology Nursing. 2005; 9: 218-238.

124. Vrijmoet-Wiersma CMJ, Kolk AM, Grootenhuis MA, Spek EM, van Klink JMM, Egeler RM, et al. Child and parental adaptation to pediatric stem cell transplantation. Supportive Care in Cancer. 2009;17(6):707-14.
125. Barrera M, Atenafu E, Hancock K. Longitudinal health-related quality of life outcomes and related factors after pediatric SCT. Bone Marrow Transplantation. 2009 Aug;44(4):249-56.
126. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. Quality of Life Research. 2008 Aug;17(6):895-913.
127. Warschburger P, Landgraf JM, Petermann F, Freidel K. Health-related quality of life in children assessed by their parents: Evaluation of the psychometric properties of the CHQ-PF50 in two German clinical samples. Quality of Life Research. 2003 May;12(3):291-301.
128. Phipps S, Srivastava DK. Repressive adaptation in children with cancer. Health Psychology. 1997 Nov;16(6):521-8.
129. Parsons SK, Shih MC, DuHamel KN, Ostroff J, Mayer DK, Austin J, et al. Maternal perspectives on children's health-related quality of life during the first year after pediatric hematopoietic stem cell transplant. Journal of Pediatric Psychology. 2006;31(10):1100-15.
130. Schwartz CE, Sprangers MAG. An introduction to quality of life assessment in oncology: The value of measuring patient-reported outcomes. American Journal of Managed Care. 2002 Dec;8(18):S550-S9.
131. Roberts CS, Turney ME, Knowles AM. Psychosocial issues of adolescents with cancer. Social Work in Health Care. 1998;27(4):3-18.
132. Enskar K, Carlsson M, Golsater M, Hamrin E. Symptom distress and life situation in adolescents with cancer. Cancer Nursing. 1997 Feb;20(1):23-33.
133. Madan-Swain A, Brown RT, Foster MA, Vega R, Byars K, Rodenberger W, et al. Identity in adolescent survivors of childhood cancer. Journal of Pediatric Psychology. 2000;25(2):105-15.
134. Pendley JS, Dahlquist LM, Dreyer Z, Wg. Body image and psychosocial adjustment in adolescent cancer survivors. Journal of Pediatric Psychology. [Article]. 1997 Feb;22(1):29-43.
135. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. Psycho-Oncology. 2009;18(2):113-27.
136. Rusiewicz A, DuHamel KN, Burkhalter J, Ostroff J, Winkel G, Scigliano E, et al. Psychological distress in long-term survivors of hematopoietic stem cell transplantation. Psycho-Oncology. 2008;17(4):329-37.
137. Clarke SA, Eiser C, Vy. Health behaviours in childhood cancer survivors: A systematic review. European Journal of Cancer. [Review]. 2007 Jun;43(9):1373-84.
138. Felder-Puig R, di Gallo A, Waldenmair M, Norden P, Winter A, Gadner H, et al. Health-related quality of life of pediatric patients receiving allogeneic stem cell or bone marrow transplantation: results of a longitudinal, multi-center study. Bone Marrow Transplantation. [Article]. 2006 Jul;38(2):119-26.
139. Michel G, Bordigoni P, Simeoni MC, Curtillet C, Hoxha S, Robitail S, et al. Health status and quality of life in long-term survivors of childhood leukaemia: the impact of haematopoietic stem cell transplantation. Bone Marrow Transplantation. 2007 Nov;40(9):897-904.

140. Barrera M, Gee C, Andrews GS, Armstrong CA, Saunders FE. Health-related quality of life of children and adolescents prior to hematopoietic progenitor cell transplantation: Diagnosis and age effects. Pediatric Blood & Cancer. 2006 Sep;47(3):320-6.
141. Lof CM, Winiarski J, Giesecke A, Ljungman P, Forinder U. Health-related quality of life in adult survivors after paediatric allo-SCT. Bone Marrow Transplantation. 2009 Mar;43(6):461-8.