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HEALTH-RELATED QUALITY
OF LIFE IN SURVIVORS OF
CHILDHOOD ACUTE
LYMPHOBLASTIC LEUKAEMIA

UNIVERSITY OF OULU,
FACULTY OF MEDICINE,
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DEPARTMENT OF NEUROLOGY;
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LIFE IN SURVIVORS OF CHILDHOOD
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LEUKAEMIA**

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Abstract

Leukemia treatment has been implicated to be responsible for a diversity of long-term adverse effects (Pui 2008), which can occur even years after diagnosis and can seriously impair survivors' performance status and quality of life (Campbell *et al.* 2007, Zeltzer *et al.* 2008). The aim of the present work was to assess health-related quality of life in long-term survivors of acute lymphoblastic leukemia (ALL), and to find out whether vocational rehabilitation can promote the coping at work of young people who take part in a training intervention or help them find employment.

Neuropsychological testing was performed on 64 survivors. Cranial irradiation had been administered to 44 of the survivors, while 20 survivors had been treated solely with chemotherapy. A control group consisted of 45 healthy young adults. We found that young adult survivors of childhood ALL treated with cranial irradiation had clear progressive deficits in their neurocognitive functioning at a mean of 20 years after diagnosis compared with healthy controls. Non-irradiated ALL survivors performed significantly better, but even they had statistically significant impairments in some of the neuropsychological test scores compared with the controls. Rand-36-Item health Survey (RAND-36) was used to assess subjective HRQoL, depressive symptoms were assessed with Beck Depression Inventory (BDI-21), and mental distress with General Health Questionnaire (GHQ-12) in 74 survivors of ALL. The control group consisted of 146 healthy young adults selected from local population registry. ALL survivors showed good HRQoL scores in comparison to the control group. Patients who had been treated for an ALL relapse and had received the most intensive chemo- and radiotherapy had significantly higher scores on mental health and vitality than the controls. Survivors of ALL report fewer depressive symptoms and equal mental well-being compared to healthy controls. Nine out of 63 survivors were selected for rehabilitation based on their occupation and psychosocial difficulties. The occupational rehabilitation course improved physical fitness and decreased overweight in long-term survivors of ALL, but impaired their HRQoL. Our findings support the idea that ALL survivors' subjective experience of well-being is possibly affected by a repressive adaptive style.

Keywords: acute lymphoblastic leukemia, childhood cancer survivor, depressive symptoms, follow-up, health-related quality of life, mental distress, neurocognitive functioning, occupational rehabilitation

Harila, Marika, Terveysteen liittyvä elämänlaatu lapsuusiässä sairastetun akuutin lymfaattisen leukemian jälkeen.

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Tiivistelmä

Leukemiahoidoilla on todettu olevan pitkäaikaisvaikutuksia (Pui 2008), jotka voivat ilmetä jopa vuosia diagnoosin jälkeen heikentäen sairaudesta selvinneiden toimintakykyä ja elämänlaatua (Campbell *et al.* 2007, Zeltzer *et al.* 2008). Tämän tutkimuksen tavoitteena oli arvioida akuutista lymfaattisesta (ALL) leukemiasta selvinneiden terveyteen liittyvää elämänlaatua pitkällä aikavälillä sekä selvittää, voidaanko ammatillisen kuntoutuksen avulla edistää interventioon osallistuneiden työssä selviytymistä tai työllistymistä.

Neuropsykologiseen tutkimukseen osallistui 64 ALL pitkäaikaiselvytyjää. Heistä 44 oli saanut pään alueen sädehoitoa ja 20 pelkästään solunsalpaajahoidoa. Verrokkiryhmässä oli 45 tervettä nuorta aikuista. Havaitsimme, että lapsuudessa pään alueen sädehoitoa saaneilla ALL-selviytyjillä oli verrokkeihin verrattuna selkeitä progressiivisia muutoksia neurokognitiivisessa toimintakyvyssä keskimäärin 20 vuotta diagnoosista. Ne, jotka eivät olleet saaneet sädehoitoa suoriutuivat huomattavasti paremmin, mutta heilläkin havaittiin tilastollisesti merkittäviä puutoksia joillakin neuropsykologisten testien osa-alueilla verrokkeihin verrattuna. 74 entisen ALL-potilaan terveyteen liittyvää elämänlaatua (HRQoL) mitattiin Rand-36 -mittarilla, masennusoireita Beckin masennustestillä (BDI-21) ja henkistä hyvinvointia General Health Questionnaire -mittarilla (GHQ-12). Verrokkiryhmäksi valittiin väestörekisteristä 146 tervettä nuorta aikuista. ALL-ryhmässä tutkittavien terveyteen liittyvää elämänlaatua mittaavat pisteet olivat hyvät verrokkiryhmään verrattuna. Ne potilaat, joita oli hoidettu leukemian uusiutumisen takia ja jotka olivat saaneet intensiivisintä solunsalpaaja- ja sädehoitoa saivat huomattavasti paremmat pisteet psyykkisen hyvinvoinnin ja vitaleisuuden osa-alueilla kuin verrokkit. ALL -selviytyjät raportoivat vähemmän masennusoireita, ja he arvioivat psyykkisen hyvinvointinsa yhtä hyväksi kuin verrokkit. Yhdeksän ALL pitkäaikaiselvytyjää osallistui heille suunnattuun ammatilliseen kuntoutus-interventioon. Ammatillinen kuntoutuskurssi paransi ALL -selviytyjien fyysistä suorituskykyä ja vähensi ylipainoa, mutta heikensi terveyteen liittyvää elämänlaatua. Tutkimustulokset tukevat ajatusta, että repressiivinen adaptaatio voi vaikuttaa lapsuusiän leukemiasta selvinneiden subjektiiviseen hyvinvoinnin kokemukseen.

Asiasanat: akuutti lymfaattinen leukemia, ammatillinen kuntoutus, henkinen hyvinvointi, kognitiivinen suoriutumisen, lapsuusiän leukemiasta selvinneet, masennusoireet, seuranta, terveyteen liittyvä elämänlaatu

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Oulu, May

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Abbreviations

ALL	Acute Lymphoblastic leukemia
ANCOVA	Univariate analyses of covariance
BDI	Beck Depression Inventory
CCSS	Childhood Cancer Survivor Study
CNS	Central nervous system
CR	Complete remission
CRT	Cranial irradiation therapy
CTCAEv3	The Common Terminology Criteria for Adverse Events, Version 3
FACT-G	Functional Assessment of Cancer Therapy-General
GHQ	General Health Questionnaire
HRQoL	Health-related quality of life
EORTC QLQ-30	European Organization for Research and Treatment on Cancer QLQ-C-30
IQ	Intelligence quotient
MCID	Minimally clinically importance difference
PIQ	Performance intelligence quotient
QOL	Qualiy of life
RAND-36	Rand-36-Item health Survey
SDRB	Socially desirable response bias
SF-36	Short-Form Health Survey
SII	The Social Insurance Institution
SN	Second neoplasm
SPSS	Statistical Package for the Social Sciences
VIQ	Verbal intelligence quotient
WHO	The Word Health Organization

List of original publications

This list is based on the following publications, which are referred to in the text by their Roman numerals I-IV:

- I Harila Marika J, Winqvist Satu, Lanning Marjatta, Bloigu Risto & Harila-Saari Arja H (2009) Progressive Neurocognitive Impairment in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 53: 156–161.
- II Harila Marika J, Salo Jarmo, Lanning Marjatta, Vilkkumaa Ilpo & Harila-Saari Arja H (2010) High Health-Related Quality of Life Among Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 55: 331–336.
- III Harila Marika J, Niinivirta Tomi IT, Winqvist Satu & Harila-Saari Arja H (2011) Low depressive symptom and mental distress scores in adult long-term survivors of childhood acute lymphoblastic leukaemia. *J Pediatr Hematol Oncol* 33(3): 194–8.
- IV Harila Marika, Haapala Eija, Vilkkumaa Ilpo & Harila-Saari Arja Efficacy of occupational rehabilitation intervention in long-term survivors of acute lymphoblastic leukemia. Manuscript

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1 Introduction

Acute Lymphoblastic leukemia (ALL) is the most common malignancy in children. Due to improvement of cancer treatments, today it has a greatly improved survival rate of approximately 80% (Gatta *et al.* 2005;2003, Gustafsson *et al.* 2000, Harras *et al.* 1996, NOPHO 2000, Pui & Evans 2006). Treatment of the central nervous system (CNS) with cranial irradiation and/or chemotherapy has been an important factor contributing to the increased survival rate. However, leukaemia treatment has been implicated to be responsible for a diversity of long-term adverse effects. (Pui 2008). CNS treatment has been suspected of being responsible for long-term neurocognitive deficits, especially when cranial irradiation is used (Campbell *et al.* 2007, Gaynon *et al.* 2000, Moore 2005). The awareness of the harmful effects of cranial irradiation therapy (CRT), especially among young children, has led to the practice of replacing it with CNS-directed chemotherapy. This includes mainly high dosage iv methotrexate and intrathecal methotrexate (Butler *et al.* 1994). Whether or not CNS chemotherapy has harmful effects on learning, and to what extent, is still controversial.

Another major concern is physical, psychosocial and educational deficits after cranial irradiation and central nervous system-directed chemotherapy, which can occur even years after diagnosis and can seriously impair survivors' performance status and quality of life (Campbell *et al.* 2007, Hill *et al.* 1998, Katon & Sullivan 1990, Moore 2005, Schultz *et al.* 2007, Zeltzer *et al.* 1997). These deficits may increase the possibility of mental distress and depression. A growing number of studies have documented the substantial impact of childhood cancer treatment which may cause impairments that diminish social functioning, including obtainment or retention of employment (Pang *et al.* 2008).

The number of ALL survivors among young adults is increasing rapidly, and the need to improve their health-related quality of life is becoming increasingly important and topical issue. Numerous studies have examined these aspects of childhood cancer, but the overall quality of life especially in long term survivors of ALL is not so well studied (Apajasalo *et al.* 1996, Elkin *et al.* 1997, Meeske *et al.* 2005, Pemberg *et al.* 2005, Stam *et al.* 2006, Zebrack & Chesler 2002). The aim in this study was to assess neuropsychological functioning, well-being, depressive symptoms and health-related quality of life and evaluate the efficacy of occupational rehabilitation on employment and coping at work in long-term survivors of acute lymphoblastic leukemia.

2 Review of the literature

2.1 Epidemiology and etiology of childhood ALL

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounting for 76–80% of all diagnoses of childhood leukemia (Gatta *et al.* 2005;2003, Gustafsson *et al.* 2000, Harras *et al.* 1996, Pui & Evans 2006, NOPHO 2000) and approximately 30% of all pediatric malignancies (NOPHO 2000).

In the Nordic countries the yearly incidence of total childhood cancer has been close to 15–20 cases per 100 000 children under 15 years of age (Gustafsson *et al.* 2000). In Finland, the yearly incidence of ALL is 50 cases per year. The incidence of childhood ALL in the Nordic countries has been stable during recent years (NOPHO 2000). The incidence of acute leukemias in Finland is about 240 new patients/year. About 20% of these are children. The peak incidence is seen at 2–5 years of age (4–5 patients/100 000). (Engholm *et al.* 2009). Boys have a higher leukemia risk than girls, but leukemia diagnosed in the first year of life is more common in girls than in boys. The incidence of ALL in white children is 3–4 per 100 000, while in African/Americans children it is consistently about half of that. (Gurney *et al.* 1995). There are substantial geographic differences in the incidence of childhood leukemia. In developed countries, the incidence rates for childhood ALL are two- to four-fold compared to the rates in developing countries, which could represent differences in environmental factors, genetic factors and diagnostic accuracy. (Greaves & Alexander 1993). In developed countries, there is a significant peak in the incidence of childhood ALL between the ages of two and five years, and one subtype, referred to as common ALL, accounts for the high incidence in this age group (Greaves 1999).

ALL is a biologically heterogeneous disorder, and its specific etiology is unknown. The causes appear to be multifactorial. Some of the factors involved in the pathogenesis of ALL include exposure to ionizing radiation or certain drugs, certain chromosome abnormalities and congenital or acquired immune deficiencies (Golub & Arceci 2002).

2.2 Treatment of childhood ALL

The cure rate for pediatric ALL has improved from 15% in the late 1960s to approximately 80% today (Gatta *et al.* 2005, Margolin *et al.* 2002). This improvement can largely be attributed to the development of more effective chemotherapeutic regimens in well-designed clinical trials, improvements in combined chemotherapy, diagnostic, surgical and radiotherapeutic techniques, refined supportive care and pediatric cancer studies and services.

Acute leukemia is treated with chemotherapy, and the specific treatment is based on the specific leukemia subtype. ALL treatment protocols also include CNS-directed therapy in the form of intrathecal administration of methotrexate and/or ARA-C given throughout the systemic chemotherapy. Chemotherapy may be supplemented with radiation therapy if there is evidence of central nervous system (CNS) leukemia or testicular leukemia. (Margolin *et al.* 2002, Pui 2008). ALL with a poor prognosis or children who suffer a recurrence of ALL may be treated with a bone marrow transplant (Margolin *et al.* 2002).

The duration of treatment varies from 24 to 36 months. A good prognosis is associated with female gender, age at diagnosis between 2 and 10 years, a low white blood cell count, and an early positive response to treatment. Children with a poor prognosis receive the most aggressive chemotherapy. ALL treatment is divided into main treatment elements: induction, consolidation and maintenance therapy. (Margolin *et al.* 2002).

Induction Treatment Phase

The first phase of ALL treatment is called induction, and it lasts 4–5 weeks. The goal of treatment is generally indicated with the term “complete remission” (CR). This is defined as resolution of the sign and symptoms of leukemia, a return to normal blood and bone marrow values, and leukemia cell kill resulting in fewer than 5% lymphoblasts in the bone marrow. The basic regimen for induction therapy includes at least a glucocorticoid (prednisone, prednisolone, or dexamethasone) and vincristine. (O’Reilly *et al.* 1996, Pui & Evans 1998). The rate of complete remission is 98% in the Nordic countries (Gustafsson *et al.* 2000).

Consolidation Treatment phase

This is the second phase of childhood ALL treatment which begins once the leukemia is in remission. Treatment includes a combination of aggressive multiagent chemotherapy, and lasts up to 6 months. Chemotherapy consists of repeated cycles of drug combinations to prevent the remaining leukemia cells from developing resistance, e.g. methotrexate and 6-mercaptopurine or 6-thioguanine, vincristine, L-asparaginase, and/or prednisone. Intrathecal therapy is continued at this time. (Margolin *et al.* 2002, O'Reilly *et al.* 1996).

Maintenance therapy

If a patient stays in remission after induction and consolidation therapy, maintenance therapy begins. The goal is to destroy any disease cells that remain so that the leukemia is completely gone. Patients at higher risk may receive more intensive maintenance chemotherapy and intrathecal therapy. Chemotherapy continues for 2–2.5 years in girls and 2.5–3 years in boys. (Margolin *et al.* 2002, O'Reilly *et al.* 1996).

2.3 Treatment-Related Late-effects

Chemotherapy, radiation therapy and stem cell transplantation can cause long-term late-effects, which are secondary conditions that arise following certain cancer treatments. Children are especially sensitive and susceptible to side effects because their tissues are still growing and developing. Side effects vary depending on which drugs are being used, how the drugs are given, and how long the drug treatment lasts. (Margolin *et al.* 2002).

Awareness of the harmful effects of cranial irradiation therapy (CRT), especially in young children, has led to the practice of replacing it with CNS-directed chemotherapy. This includes mainly high dosage and intrathecal methotrexate. (Butler *et al.* 1994, Campell *et al.* 2007, Gaynon *et al.* 2000, Moore 2005, Mulhern & Palmer 2003, Oeffinger *et al.* 2006).

2.3.1 Physical long-term late effects

Reports in the literature indicate that approximately 75% of survivors have one or more late effects (Cardous-Ubbink *et al.* 2004). The most common late effects are

those of growth and development, including linear growth velocity, intellectual development, and sexual maturation (Adan *et al.* 2001). A recent study of adult survivors of childhood cancer reported that 62% have at least one chronic health condition, with 25% reporting conditions considered to be severe or life-threatening (Oeffinger *et al.* 2006), which may not be manifest until many years later.

The Childhood Cancer Survivor (CCSS) study cohort provides the largest and most comprehensive assessment of the health of childhood ALL survivors, and in this analysis spanning more than 20 years from diagnosis adult survivors – including nonirradiated, nonrelapsed ones – reported excessive chronic health issues and poor health status, with ALL survivors being one of the highest risk groups for late mortality and morbidity. (Mertens *et al.* 2001, Mody *et al.* 2008).

These morbidities include second neoplasms, cardiac toxicity, infertility, neurologic toxicity, growth failure and neurocognitive dysfunction. Second neoplasms (SNs) are one of the most serious and devastating morbidities associated with cancer therapy and have been strongly associated with the use of therapeutic radiation for treatment of the original cancer. (Jenkinson *et al.* 2004, Mertens *et al.* 2001, Mody *et al.* 2008, Neglia *et al.* 2001). MacArthur *et al.* (2007) showed that survivors whose ALL had recurred within 5 years of diagnosis had a 61-fold higher likelihood of dying compared with the general population. Mody *et al.* (2008) also found mortality risk – higher in the relapsed group – but they found lower overall likelihood of death.

Several recent studies have shown that survivors of leukemia have an increased risk of developing CNS tumors that are associated with radiotherapy (Banerjee *et al.* 2009, Goshen *et al.* 2007, Neglia *et al.* 2006;1991, Phillips *et al.* 2005, Pui *et al.* 2003, Paakko *et al.* 1994). Meningiomas and gliomas appear to be the most common latent brain tumors in leukemia survivors. In the study of Banerjee *et al.* (2009) meningiomas occurred in more than one-fifth (22%) of the 49 cranially irradiated long-term survivors of childhood leukemia who had been followed for a median of 21 years. Goshen *et al.* (2007) reported a 17% incidence of meningiomas in irradiated patients.

2.3.2 Neuropsychological long-term late effects

More effective and aggressive medical treatments are often associated with neurocognitive morbidity. Long-term survivors of leukemia treated during childhood are at risk of neuropsychological late effects, which represent an

extremely well studied topic. Higher dose of CNS radiation, therapy with high-dose systemic or intrathecal methotrexate or cytarabine, younger age at treatment and female gender are generally associated with great risk of neurocognitive late effects. (Fouladi *et al.* 2005, Hertzberg *et al.* 1997, Ochs *et al.* 1991, Waber *et al.* 1995). Different mechanisms have been postulated to explain the underlying neurological basis of neurocognitive dysfunction. Hippocampal dysfunction may be a causal mechanism underlying aspects of these neuropsychological sequelae. Located in the medial temporal lobes, the hippocampal formation plays a central role in learning and memory - functions prominently affected by radiation. (Zola-Morgan & Squire 1993). Recent studies have brought up damage to cortical and subcortical white matter (Mulhern *et al.* 2000, Steen *et al.* 2001). Iuvone *et al.* (2002) reported that up to 50% of children treated with a combination of CRT and IT methotrexate show changes in white matter that are generally progressive and do not resolve.

Two seminal studies set the stage for three decades of research on the neurocognitive impact of irradiation and chemotherapy applied to the CNS. Initially, Soni *et al.* (1975) reported that CNS prophylactic treatment for patients with Acute Lymphocytic Leukemia (ALL) did not impact intellectual functioning. The dose of cranial radiation therapy (CRT) in this study was 24 Gy, the standard prophylaxis at that time. Soon after that, Meadows *et al.* (1981) reported results that were diametrically opposed to the previous study. At the same dose of CRT, it was noted that pediatric ALL patients suffered declines in intellectual development. These two studies stimulated intensive research efforts designed to identify whether or not irradiation and chemotherapy to the brain resulted in neurocognitive impairment in pediatric patients. As research progressed, risk factors began to become apparent, and at present we understand the likely nature of neurocognitive involvement in this population. (Meadows *et al.* 1981).

Adverse neurocognitive outcomes reported in the literature are declines in overall intellectual ability (Mulhern *et al.* 1992), academic performance (Anderson *et al.* 2000), memory and learning (Hill *et al.* 1997), attention and concentration (Lockwood *et al.* 1999), information processing speed (Cousens *et al.* 1991), visuospatial skills (Espy *et al.* 2001), psychomotor functioning (Kaleita *et al.* 1999), and executive functioning (Anderson *et al.* 1997).

The majority of the cross-sectional studies report that combined prophylactic treatment, CNS chemotherapy and cranial irradiation is associated with intellectual impairment. Children who have survived leukemia typically obtain lower IQ scores than matched healthy children. (Anderson *et al.* 1994, Dowell *et*

al. 1991, Said *et al.* 1989). A meta-analysis by Cousens *et al.* (1988) reviewed 30 studies reporting cognitive function in children after cranial irradiation for ALL. Decrements were found in intellectual function, amounting to around 2/3 of a standard deviation (10 IQ points) in ALL survivors treated with cranial irradiation compared to controls (Cousens *et al.* 1988). Prospective studies, in which children were assessed at diagnosis and follow-up intervals (Berg *et al.* 1983, Meadows *et al.* 1984;1981, Mulhern *et al.* 1991, Rubenstein *et al.* 1990, Stehbens & Kisker, 1984), have given mixed results. These studies differ on a number of dimensions, which may explain their variable findings.

Combined prophylactic treatment has also been linked to deficits in fine motor skills, visual-spatial abilities, verbal and nonverbal memory, psychomotor speed and shifting of attention, auditory perception, word fluency, contingency naming, and the ability to follow directions (e.g., Cousens *et al.* 1991, Dowell *et al.* 1991, Jannoun & Chessells 1987, Mulhern *et al.* 1988). Academic difficulties are evident in parent and teacher reports of school performance and scores on standardized tests of achievement (Mulhern *et al.* 1991).

Findings support the idea that the cognitive deficits of CNS chemotherapy given without cranial irradiation are less harmful, but it is still controversial (Dowell *et al.* 1991, Pfefferbaum-Levine *et al.* 1984, Rowland *et al.* 1984). Evidence suggests that children who received combined prophylactic therapy should perform more poorly on measures of cognitive and academic functioning than those who received CNS chemotherapy only. Some studies have failed to find any evidence of lower IQ, deficits in neuropsychological functioning, or academic difficulties (e.g., Copeland *et al.* 1996, MacLean *et al.* 1995, Mulhern *et al.* 1992). Other studies report lower Verbal and Full Scale IQ scores, memory problems, impaired performance on tasks involving simultaneous processing, deficits in the areas of motor performance, attention, and symbolic manipulation, and poorer academic performance (Brown *et al.* 1992a, Ochs *et al.* 1991).

Randomized studies have been unable to find a difference between irradiated and non-irradiated ALL patients (Waber *et al.* 2007), while several non-randomized controlled studies have shown impairments in cognitive functions compared with controls. The defects have been milder when chemotherapy has been used without cranial irradiation. (Copeland *et al.* 1996, Moleski 2000, Waber *et al.* 2000, Butler & Copeland 1993).

Reviews of studies suggest that at least 30% of the survivors exhibit some degree of impairment. Deficits involve vigilance attention, working memory, spatial awareness, processing speed, self-monitoring (Butler *et al.* 1999;1994,

Mulhern & Butler, 2004; 2006, Moleski 2000, Spiegler *et al.* 2004), performance IQ (PIQ) (Raymond-Speden *et al.* 2000), fine motor skills and nonverbal memory (Peterson *et al.* 2008). Campbell *et al.* (2007) performed a meta-analysis of 28 studies published up to 2004, including studies in which CNS treatment for childhood ALL involved cranial irradiation, as well as studies in which treatment consisted of chemotherapy only. Clinically significant deficits were reported in specific neurocognitive abilities, such as attention and speed of information processing and areas of executive functioning. (Campbell *et al.* 2007). A meta-analysis of chemotherapy-treated subjects by Peterson *et al.* (2008) indicated defects in intelligence, academic achievement, information processing speed, verbal memory, executive functioning and fine motor skills compared with controls. Mennes *et al.* (2005) concluded that children treated for ALL with chemotherapy are only impaired in selective aspects of cognitive functioning: attention, concentration and information processing speed. Buizer *et al.* (2009) reviewed twenty-one studies published since 1997 that included an ALL group treated with chemotherapy only and a control group. There is evidence of subtle long-term neurocognitive deficits in survivors of childhood ALL after treatment with chemotherapy only. The deficits are mainly present in basic neuropsychological processes of attention and executive functioning, while global intellectual function is relatively well preserved. (Buizer *et al.* 2009).

Adverse effects typically emerge within 1 to 2 years of administration, but some studies have observed that cognitive disturbances may be delayed up to 10 years after treatment (Jankovic *et al.* 1994, Kato *et al.* 1993). A decline in intellectual functioning has been shown 4–8.5 years after treatment with 18-24 Gy of CRT, whereas some longitudinal evaluations did not support the expected hypothesis that ALL treatment results in cognitive deterioration over time. Patients who have been treated with cranial irradiation have been reported to have a significant decline in full-scale IQ, the decline of IQ being more prominent with time from diagnosis. (Cousens *et al.* 1988, Jankovic *et al.* 1994). The only previous study on very-long-term ALL survivors after more than 10 years of cranial irradiation reported significant neuropsychological deficits compared with healthy controls (Kato *et al.* 1993). Link *et al.* (2006) investigating 44 adults with a mean age of 25 years treated for childhood ALL showed impaired neuropsychological capacity in the period 8–27 years after CRT. A decline in one or more aspects of cognitive functioning after treatment with chemotherapy is reported in only approximately two thirds of ALL studies (Moleski 2000).

2.4 Health related quality of life (HRQoL)

2.4.1 Definition

In the last three decades, the quality of life of children treated for cancer has become a major focus in the field of pediatric oncology (Levi 2006). There is no consensus on the definition of quality of life. Definitions range from describing the quality of life impact of a person's health on his or her ability to lead a fulfilling life (Bullinger 1993) to those with a holistic emphasis - social, emotional, and physical well-being (Greer 1984). A number of definitions proposed by various authors as to the exact nature of QoL are shown in Table 1.

Table 1. Definitions of QoL.

Number	Definition
I	QoL is defined as an individual's overall satisfaction with life and general sense of personal well-being (Schipper & Clinch 1988).
II	QoL is the state of well being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease (Gotay <i>et al.</i> 1992).
III	QoL refers to patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal (Cella 1992).
IV	QoL is patient perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (WHOQOL 1994).

The World Health Organization (WHO) defines quality of life as "the individual's perception of his/her position in life, within the cultural context and the values in which he/she lives, as well as relation to his/her objectives, expectations, standards and concerns". According to WHO, QoL consist of physical, mental/emotional and social domains, which is referred to as health-related quality of life (HRQoL) (WHOQOL Group 1994). The WHO definition has influenced the notion of HRQoL as a multidimensional concept.

As well taking into account the impact of health on QoL, HRQoL includes other domains of life functioning that are also affected by health/illness states. In HRQoL dimensions, physical functioning refers to one's ability to perform various activities at the most basic level of daily living. Social functioning typically refers to a person's ability to interact with family and friends and to maintain social roles. Emotional functioning is commonly assessed as the

negative effects of illness, such as depression or anxiety. Cognitive functioning refers to memory or the ability to concentrate. Life satisfaction represents a person's overall sense of well-being. (Aalto 1999).

2.4.2 Measuring HRQoL outcomes

The assessment of quality of life is used when studying the impact of various health problems and illness on different domains of life, when monitoring the health status of population groups and assessing alternative health-care methods and their costs (Aalto 1999).

In accordance with the WHO definition, HRQoL indicators often have at least three main dimensions: physical, mental and social well-being (WHOQOL Group 1994). Different indicators also contain complementary dimensions, such as self-perceived health, energy/vitality (Aalto 1999, Hays *et al.* 1993, Ware & Sherbourne 1992), sexual functioning, spiritual well-being and vocational or role performance (Dibble *et al.* 1998, Ness *et al.* 1998, Osoba *et al.* 1994).

In health-related quality of life research, the indicators that are used are usually divided into disease-specific indicators and those assessing general HRQoL (e.g. Kind 2001). Disease-specific indicators assess the domains of quality of life that are of key significance for a specific disease. General indicators can be used to assess differences in QoL between different population groups, patient groups and in unselected population. (Kind 2001). QoL indicators can also be classified, according to measurement level, to one-dimensional indicators, which only assess one dimension of QoL; global indicators describing QoL on a general level, for example on a scale from 0 to 100 or with the aid of a single question (e.g. "How would you assess your quality of life?"); multidimensional profile indicators, which describe QoL with several dimensions, with the results given as QoL profiles, and single preference indicators, where different QoL domains are expressed with a single index. (Coons *et al.* 2000).

Since the 1980s, several indicators have been developed for the measurement of functional and health-related QoL (Cieza & Stucki 2005, Gill & Feinstein 1994). The most widely used indicators in Finland are 15D (Sintonen 2001), Nottingham Health Profile (Koivukangas *et al.* 1995) and the Rand 36-item Health Survey 1.0 (Aalto *et al.* 1995, Hays *et al.* 1993). Some of the more commonly used measures in cancer patients are Short Form 36 (SF-36), European Organization for Research and Treatment on Cancer QLQ-C-30 (EORTC QLQ-30), Functional Assessment of Cancer Therapy-General (FACT-G). It is thought

that the internationally most commonly used HRQoL measure, RAND-36 (SF-36) works reliably among the Finnish population. (Aalto 1999).

2.4.3 Model to explain the results of HRQoL

Good levels of physical and mental functioning and general health status have long been associated with well-being and overall quality of life, while illness has the opposite effect (Bowling 1995). A common assumption of HRQoL research is that the HRQL of survivors will decline as a function of late effects of medical treatment (Spieth & Harris 1996, Varni *et al.* 2002). It is supposed when adverse outcomes increase, the patient's quality of life will decrease. However, because self-report of HRQoL is subjective, there are a number of individual factors that might contribute to the observed outcomes, and adaptive style is hypothesized to be one of a significant determinant of HRQoL. (Phipps 2007).

Almost a decade ago Albrecht and Devlieger (1999) addressed the question: "Why do many people with serious and persistent disabilities report that they experience a good or excellent QoL (quality of life) when to most external observers these people seem to live an undesirable daily existence?" (Albrecht & Devlieger 1999, p 977). This is known as the "disability paradox." The authors assumed that those who experience suffer and lost replace their losts with new meanings in their lives. Living becomes thus richer and more satisfying. Childhood experiences lead to better appreciation of being alive and to considering possible impairments of the present health status less important. Especially those survivors who perceived their health as better than what would be expected based on objective medical findings ("paradox of satisfaction"), could belong to the so-called repressors who tend to presents themselves in a favourable light. The results could possible be explained by denial mechanism of the long-term cancer survivors compensating and overcompensating extant late effects. (Albrecht & Devlieger 1999). Some authors suggest that defensiveness is a combination of self-deception, which represents an intrapsychic process associated with defensiveness and impression management reflects the motivation to present oneself in a positive manner, rather than real defensiveness (O'Learly 2007).

Response shift theory (the idea that the terms of reference by which quality of life is judged change over time) helps in understanding the so-called disability paradox. Response shift is a natural way in which individuals who are confronted with a serious illness adapt and cope with changes in physical health (eg.

Postulart & Adang 2000, Lepore & Eton 2000), and it influences the measures of change of HRQoL. People actively construct meaning from the environment, and display a range of cognitive mechanisms to continually adapt to changing circumstances. People can adjust the way they think about their life when they encounter relevant new information. Response shift refers to a change in the meaning of one's evaluation of a construct as a result of a change in one's internal standards of measurement, a change in one's values, or a change in one's definition of the construct. (Sprangers & Schwartz 1999).

The majority of published studies have shown that children with cancer report low depressive symptom levels, in many cases even significantly lower than either test norms or healthy controls. Canning *et al.* (1992) were the first to assess adaptive style in children with cancer as a possible explanation for bias in self-report. They documented a high prevalence of repressive adaptive style in children with cancer, which explained, in part, the low levels of self-reported depressive symptoms in their cancer sample. In a large cross-sectional sample of children and adolescents with cancer, Phipps (1997) show that the incidence of repressive adaptive style in the cancer group was double that of healthy controls (36–18%), conversely cancer group demonstrated low levels of a “high anxious” style relative to healthy controls. These findings have been replicated several times by others research, both in children with cancer and long-term childhood cancer survivors (Erickson & Steiner 2001, Jurbergs *et al.* 2007, Phipps *et al.* 2001).

2.5 Quality of life among ALL survivors

Research has suggested that the perception of psychosocial well-being influences physical functioning and treatment outcomes among adolescents with cancer, and those experiences during treatment and individual responses to treatment have an effect on HRQoL in survivorship.

Survivors who report physical late effects also demonstrate less positive psychosocial outcomes (Zebrack & Chesler 2002). Depression is associated with increased functional impairment and poorer quality of life over the course of chronic illness (Katon & Sullivan 1990, Weitzer *et al.* 1990). Long-term survivors of childhood leukemia have been reported to have increased risk for psychological problems, depression, anxiety and negative mood compared with siblings (Schultz *et al.* 2007, Zebrack & Chesler 2002, Zeltzer *et al.* 1997). However, a recent study found that the majority of survivors do not appear to

suffer mentally from their illness (McDougall & Tsonis 2009). Many studies report equal or only small differences in psychological well-being between survivors and control group (Eiser 2004, Kazak *et al.* 2010, Stam *et al.* 2001). For example, in a large, sibling-controlled study of young adult survivors of childhood leukemia, Hodgkin's disease and non-Hodgkin's lymphoma, Zebrack *et al.* (2002) found that survivors had a significantly increased risk for reporting symptoms of depression and somatic distress, but the rates fell within the population norms. Some studies report even higher psychological well-being compared to general population. In a report from the Childhood Cancer Survivor Study Zelzer *et al.* (2008) found that the survivors had better scores for depression, anxiety and global distress compared to the population norms. Pemberger *et al.* found (2005) less depression in a group of 78 childhood cancer survivors than the population norms. An increased risk for emotional problems in childhood cancer survivors has been shown to be associated with female gender, older age at follow-up, cranial irradiation, a greater number of relapses and the presence of severe functional impairment (Stam *et al.* 2006).

Chronic adverse health effects of the disease and treatment are common among long-term survivors (Geenen *et al.* 2007, Hudson *et al.* 2003, Robison *et al.* 2005, Stevensen 1998). A recent study by Oeffinger *et al.* (2006) found that 62% have at least one chronic health condition, 25% reporting conditions considered to be severe or life-threatening. Despite physical late effects, the majority of survivors do not appear to suffer negatively from their illness experience (Zebrack & Chesler 2002).

Reviews by Langeveld *et al.* (2002) and Eiser *et al.* (2000) indicated that survivors are in good physical health and functioning well psychologically and socially. Survivors do not differ in terms anxiety or depression when compared with population norms and matched controls (Eiser *et al.* 2000). Some studies reported that long-term childhood cancer survivors show comparable or even higher-than-average positive subjective rating of the various areas of HRQoL (Pemberger *et al.* 2005, Apajasalo *et al.* 1996, Gray *et al.* 1992, Langeveld *et al.* 2004, Maunsell *et al.* 2006). A review by McDougall & Tsonis (2009) shows that in general, cancer survivors score similarly to controls on the physical, psychological and social domains of QoL/HRQoL, the greatest differences being found in physical well-being.

Maunsell *et al.* (2006) compared 1334 survivors aged 15 to 37 years to an age- and sex-matched comparison group, and found small significant differences with respect to general health and physical functioning, but no significant

differences in psychological functioning. Survivors had significantly poorer ratings than population samples or matched comparison groups with respect to role limitations due to physical functioning, as was also seen in the studies by Stam (2006). Using a sample of 7147 cancer survivors aged 18 to 54 years, Zeltzer *et al.* (2008) found that survivors had an increased risk of lower HRQoL than US population norms regarding physical functioning, general health, vitality and overall physical functioning. Survivors had higher scores than the general US population on a mental health subscale and did not differ from the norm on a mental health component summary. Survivors reported significantly poorer ratings regarding role limitations due to emotional functioning. Langeveld *et al.* (2004) reported that 400 survivors aged 16 to 49 years scored significantly lower for physical functioning than an age-matched comparison group, but scored higher on vitality and general health. Blaauwbroek *et al.* (2007), Stam *et al.* (2006) and Zeltzer *et al.* (2008) showed that survivors scored significantly poorer on subscales of social well-being.

Previous studies on long-term ALL survivors have reported lower (Stam *et al.* 2006, Blaauwbroek *et al.* 2007, Grant *et al.* 2006), higher (Apajasalo *et al.* 1996, Pemberger *et al.* 2005, Zeltzer *et al.* 2008) or similar (Langeveld *et al.* 2004, Maunsell *et al.* 2006) ratings for HRQoL/QoL when compared with population norms or matched comparison groups. Despite the varying results of the previous studies among long-term ALL survivors, generally the survivors' measured HRQoL is considered good. In a large Childhood Cancer Survivor Study (CCSS) Zeltzer *et al.* (2008) found lower scores among leukemia survivors compared to U.S. population norms on all other subscales in SF-36 except mental health, where the survivors obtained higher scores. Instead, a large Canadian study found very little difference in QoL scores between leukemia survivors and population controls. Significantly lower scores were found only in the SF-36 subscale of physical role (Maunsell *et al.* 2006). Meeske *et al.* (2005) found better HRQoL measured by RAND-36 in non-fatigued ALL survivors, but lower HRQoL in fatigued survivors in comparison to population norms. Significantly higher scores were found on the subscales of vitality, mental health and role limitations due to emotional problems. Survivors who suffered from fatigue had lower QoL than population norms. (Meeske *et al.* 2005).

Blaauwbroek *et al.* (2007) reported no difference in HRQoL measured by RAND-36 in long-term ALL survivors compared to population norms. Very long-term follow-up had significantly lower scores than population sample on physical and social functioning, vitality and general health (Blaauwbroek *et al.* 2007). In

their long term (25 years) study based on a CCSS cohort, Mody *et al.* (2008) found that ALL survivors reported more adverse general health and mental health, functional impairments, and activity limitations compared with siblings. Survivors who received radiation in their treatment or had a leukemia relapse were found to be at greatest risk for adverse outcome (Mody *et al.* 2008).

2.5.1 Social outcomes

The results of a recent study suggest that childhood cancer survivors generally have similar high school graduation rates as their sibling counterparts (Gurney *et al.* 2009). Some studies reported no difference in scholastic achievement between leukemia patients and healthy controls (Haupt *et al.* 1994, Koch *et al.* 2004), whereas others found irradiated leukemia patients to have more in need of special education, compared with their siblings, controls or nonirradiated survivors (Barrera *et al.* 2005, Gurney *et al.* 2009, Mitby *et al.* 2003). Mitby *et al.* (2003) reported that the use of special education services among 12 430 participating survivors was 23%, in contrast to only 8% among 3410 siblings. College graduation rates were also lower among 25- to 49-year-old survivors of acute lymphoblastic leukemia (ALL; 38%) than in the sibling group of comparable age (48%) (Mitby *et al.* 2003). Harila-Saari *et al.* (2007) found that nearly ALL leukemia survivors complete basic education in Finland, but that patients treated with cranial irradiation and females treated with chemotherapy under the age 7 had lower grades.

The survivors at greatest risk for use of special education services were those diagnosed at 5 years of age or younger, while the use of intrathecal methotrexate and/or cranial radiation significantly increased the likelihood that a survivor would later use special education services. Survivors are slightly less likely than expected to attend college, and are more likely to be unemployed and not married as young adults. (Gurney *et al.* 2009, Mitby *et al.* 2003, Frobisher *et al.* 2007). An analysis of 1206 survivors of ALL survivors aged 25 to 49 years revealed that only 55% had ever been married, compared to 69% of CCSS siblings ($P < .001$). Females treated with cranial radiation therapy were at increased risk of never having married. (Mody *et al.* 2008). Unmarried/divorced survivors report significantly higher limitations in functioning and lower quality of mental health than do survivors who are married. A lower quality of mental health was also reported more commonly by those survivors who did not graduate from high school. (Zeltzer *et al.* 2008).

2.5.2 Employment

Result from the CCSS study indicate that chronic medical conditions increase the risk for unemployment (Pang *et al.* 2008), which may result in a lower quality of life. Zeltzer *et al.* (2008) found that survivors seeking work or who are unable to work were at increased risk for symptoms of depression, anxiety and somatic distress compared with employed survivors.

According to one estimate, 16.8% of working-age survivors are unable to work because of physical, mental or emotional problems; of those who can work, 7.4% were limited in the kind or amount of work they could do (Hewitt *et al.* 2003). A recent meta-analysis showed that adult survivors of childhood cancer are twice as likely to be unemployed compared to healthy controls (de Boer *et al.* 2006). In a large Childhood Cancer Survivor Study (CCSS) Kirchhoff *et al.* (2010) found that childhood cancer survivors reported health-related unemployment more often (10.4%) than siblings. Meta-analysis of controlled studies the unemployment rate was average 22%, respectively uncontrolled studies 30% for leukemia survivors (de Boer *et al.* 2006). Several studies show that especially survivors of CNS cancer are at risk of unemployment; they are nearly 5 times more likely to be unemployed as adults than the control group, but no difference was found between patients and controls in Europe (de Boer *et al.* 2006). Zeltzer *et al.* (1997) found that survivors of ALL had not enjoyed higher education, were unemployed or were working less than half the time compared to sibling controls. Higher unemployment rates were found among the women in the irradiated group than in the age- and sex-matched general population (Zebrack & Chesler 2002). In a cross-sectional case-control study, 30 young-adult survivors of childhood cancer -mainly lymphoma and ALL- did not differ from vocational and educational adjustment compared to healthy controls and general population norms (Boman & Bodeg ar 2004). A Swedish national cohort study found that non-central nervous system (CNS) cancer survivors had similar education and employment status as the general population, in contrast survivors of CNS tumors (Boman *et al.* 2010).

To summarize the findings, adult childhood cancer survivors are at elevated risk for unemployment. Consistent with education risk, the risk of unemployment is potentiated among those who were treated with high doses of cranial radiation, those diagnosed at a young age, females, and those with chronic medical conditions.

2.5.3 Vocational rehabilitation

In recent years, the scope of the concept of rehabilitation has widened to encompass promotion of life control, in addition to improved work and functional ability. In the Government Resolution on Rehabilitation (2002, 2) rehabilitation is described as a “process of changes of a person, or a person and the environment, which aims at promoting functional ability, independent coping, well-being and employment. Rehabilitation is planned and multiprofessional, often long-term action aimed at helping rehabilitees to control their own life situation”.

With the aid of vocational rehabilitation measures, the aim is to improve rehabilitees’ vocational skills and work ability and promote their employment and integration into the job market and society. Rehabilitation is implemented as a long-term process, either individually or in a group, based on individual rehabilitation needs.

In Finland, the Social Insurance Institution (SII) has a key role in arranging vocational rehabilitation. This is based on the 1991 Act, which was last amended in 2005 (Act 15 July 2005/566). According to the Act, those insured have the right to appropriate vocation rehabilitation if illness, damage or injury poses a threat of disability, or if the person’s work ability and earning possibilities must be considered to be significantly impaired due to illness, damage or injury. Threat of work disability refers in legislation to a situation where it is likely, without vocational rehabilitation, that the insured person will in the near future be granted disability pension, even when taking into account the possibilities provided by treatment and medical rehabilitation. (Act 15 July 2005/566).

”The aim of rehabilitation arranged by SII is to provide such medical or vocational rehabilitation which responds to the rehabilitee’s needs and society’s demands, is reliable and sage, and with the aid of which eligible rehabilitees’ work and functional ability can be maintained and promoted” (SII 2003. 2).

Understanding rehabilitees’ rehabilitation needs calls for comprehensive and versatile clarification of the individuals’ situation as a whole (Järvikoski 2008, Suikkanen and Lindh 2001a, Talo *et al.* 1992). Based on this, individuals’ physical, mental and social preconditions for coping at work are charted, in addition to their state of health (Talo *et al.* 1992), and considered in relation to their life situation. The starting point of rehabilitation need may be the individual’s subjective assessment of need of change or a self-perceived problem

he/she needs help with. The starting point of expert evaluation is assessing whether the problem is of such type and severity that it warrants launching rehabilitation measures. Individual subjective rehabilitation need and expert evaluation of rehabilitation need are not always compatible. (Järvikoski 2008, Järvikoski & Härkäpää 2005e; 2001a). Identifying rehabilitation need may also be based on a multiprofessional joint assessment of the individual's situation conducted in collaboration with the applicant, where indicators measuring physical, mental and social functioning are used in addition to interviews (Mäkitalo *et al.* 2008, Rissanen 2008).

Vocational rehabilitation interventions have not been conducted earlier among long-term ALL survivors. There is only one study looking at the effects of rehabilitation (chiropractic services) on physical functioning and HRQoL among all childhood cancer survivors with severe late effects. The study concluded that long-term childhood cancer survivors do not appear to utilize rehabilitation services to optimize their physical functioning and to increase their HRQoL. (Montgomery *et al.* 2011).

3 Aims of the study

The main purpose of this study was assess the longitudinal adverse treatment related neuropsychological late-effects and Health related quality of life (HRQoL) among long-term ALL childhood cancer survivor. The numbers I-IV hereafter refer to the original publications. The specific aims of the individual studies were:

1. To assess neuropsychological functioning in a population-based cohort of young adult childhood ALL survivors. (I)
2. To assess Health-related quality of life (HRQoL) in a cohort of long-term childhood acute lymphoblastic leukemia (ALL) survivors. (II)
3. To examine the prevalence of depressive symptoms and mental well-being in adult long-term survivors of childhood acute lymphoblastic leukaemia (ALL) at a mean of 20 years after the cessation of therapy. (III)
4. To evaluated efficacy of occupational rehabilitation on employment and coping at work in long term survivors of acute lymphoblastic leukemia who had psychosocial or/and employment problems. (IV)

4 Subjects and methods

4.1 Study design

This study is a substudy of a larger research project on the late effects of childhood leukemia treatment being conducted at the Department of Pediatrics in Oulu University Hospital during the years 2002–2005.

The survivors and controls were invited to participate in the study by a letter. If they agreed they were invited to the clinic for a two-day late-effect study, which included neuropsychological/psychological examination and an interview performed by a psychologist (M.H.) and a careful review of medical history and clinical examination to evaluate the physical late effects performed by a paediatrician. The participants brought copies of their medical records if they had been treated in other hospitals. When needed, copies of patient files were ordered from other hospitals with the participant's permission. Before the visit the participants filled in several questionnaires, which were sent to them by mail. Participants who were unable to come to the hospital answered and sent the questionnaires by mail and took part in a telephone interview. For them no grading of physical late-effects was performed. Based on the responses the need for rehabilitation was evaluated by examiners and an expert group from a rehabilitation center. Survivors in need of rehabilitation due to occupational or psychosocial problems were provided a possibility to participate in occupational rehabilitation. Study population is presented schematically in Figure 1.

The rehabilitation course was planned in collaboration with pediatric oncology experts at the Department of Pediatrics and Adolescence, Oulu University Hospital, and Merikoski Rehabilitation and Research Center. The practical arrangement of the rehabilitation course was carried out by an occupational rehabilitation team at the Merikoski Rehabilitation and Research Center. The team consisted of a social worker, 2 rehabilitation nurses, a physiotherapist, a psychologist, two rehabilitation doctors, an occupational therapist and an IT-counsellor.

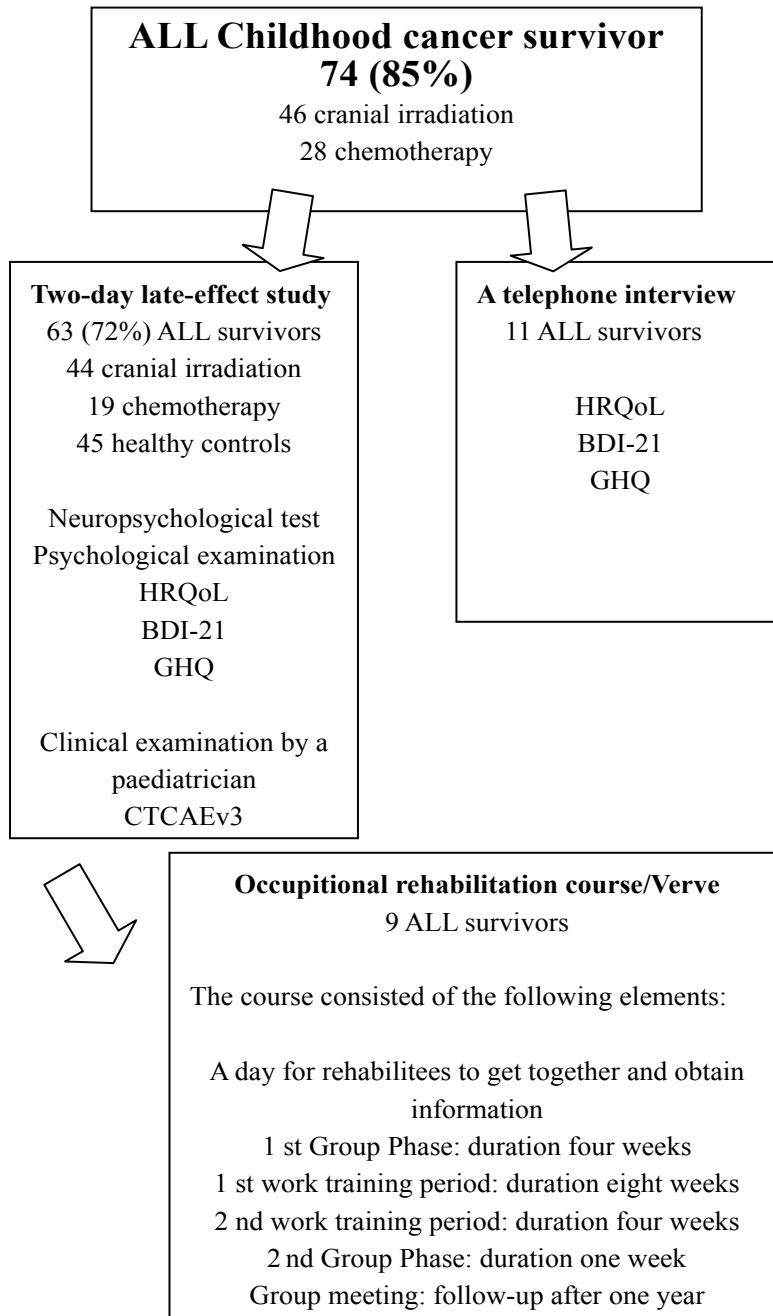


Fig. 1. Study population.

The course was carried out on outpatient basis, so that rehabilitation resembled normal work. The course included an open group phase, work training and individual monitoring days. Overnight accommodation was arranged for participants coming from further away. Rehabilitation services were not available during weekends, but when needed, all-inclusive accommodation was available for rehabilitees coming from other areas.

The content of the rehabilitation program was dictated by a weekly plan that was initially drawn up jointly with the rehabilitees during a get-together and planning event, about one month prior to the onset of the course. A group meeting was arranged one year after the end of the rehabilitation course. The course comprised both group and individual session, with focus on resources, activity and team spirit as some of the guiding principles. A personal tutor and rehabilitation nurse were in charge of one-on-one discussions. Individual work training took place in workplaces. The program also comprised phone counseling, workplace visits and home visits when needed. The course consisted of elements shown in table 2.

Table 2. The course consisted of elements.

Duration	Content
A day for rehabilitees	to get together and obtain information
1st Group Phase	
Week 1	team building, the elements of functional ability (physical, mental and social)
Week 2	life control as a concept and in everyday life
Week 3	vocations in relation to one's own wishes and abilities
Week 4	preparing for work training
1st work training period	duration eight weeks
Summer break	
2nd work training period	duration four weeks, assessment by superior, rehabilitee's own assessment
2nd Group Phase	duration one week
Week 5	drawing up a plan for the future, plan drawn up by the rehabilitee, individual rehabilitation journal
Group meeting:	follow-up

The main purpose of the rehabilitation intervention was to improve, with the aid of occupational coaching, survivors' possibility to become employed directly after occupational training or find suitable vocational education or employment through work training. Comprehensive evaluation of survivors' rehabilitation preconditions and potential was performed. Based on the evaluations an

individual occupational rehabilitation plan was created, taking into account the survivor's physical, psychological and social restrictions.

The course aimed at recognition of the rehabilitees' own strengths and resources, better life control, social skills and activity, as well as increasing physical fitness and activity.

4.2 Subjects

This study included all young adult survivors of ALL treated at Oulu University Hospital in 1971–1994 who were at least 18 years old within 6 months of the invitation, and who had been diagnosed at least 10 years earlier, had no evidence of leukaemia at the time of the evaluation, and were living in Finland. Patients with Down's syndrome (one), severe mental retardation (one), severe brain injury caused by an accident (one) or deficient Finnish language skills (one case) were excluded. A total of 87 young adult survivors fulfilled the inclusion criteria, two of whom were lost from the follow-up. From the 87 survivors that fulfilled the inclusion criteria 74 (85%) agreed to participate in the study. Sixty-three of them (72% of all who fulfilled the inclusion criteria) agreed to participate in a two-day examination visit at the hospital. The remaining 11 participants agreed to a telephone interview and filled in questionnaires. The study participants did not differ from the 13 non-participants in terms of gender, age at diagnosis or treatment. The study is part of a larger late-effect study. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Oulu.

Of the 74 survivors (26 male), 46 had been treated with cranial irradiation and chemotherapy while 28 had solely been treated with chemotherapy. The mean follow-up time since diagnosis was 20 years (range 10–32 years). Ten patients had been successfully treated for a relapse and one patient had undergone bone marrow transplantation (BMT) in the first remission. The baseline characteristics of the study population are shown in Table 3.

The dose of cranial irradiation was 18-23 Gy (16 patients), 24-25 Gy (23 patients) or 30-48 Gy (7 patients, 4 of whom had been irradiated twice). The patients were treated according to several different ALL protocols used from 1972 to 1992. The common Nordic protocols were used from 1992 onwards. The CNS treatment in the non-irradiated patient group included mainly intrathecal methotrexate and high-dose intravenous methotrexate. The Nordic ALL protocols have previously been presented in detail (Gustafsson *et al.* 2000).

The controls

As a control group we had 45 (20 men) healthy persons. They were selected at random from the local population registry for our earlier study (Winqvist *et al.* 2001). The controls did not differ in age, gender or education from the ALL survivors. (I)

Table 3. Participants' characteristics.

Variable	ALL Survivors (n=74)	Irradiated (n=46)	Non-irradiated (n=28)	Controls (n=146)
Mean age at study, years (range)	24 (17-37)	25 (17-37)	21 (17-32)	25 (17-37)
Mean age at diagnosis, years (range)	5 (0-15)	5 (0-15)	5 (0-15)	-
Time since diagnosis, years (range)	20 (10-32)	21 (10-32)	18 (11-24)	-
Male	26 (35%)	17 (37%)	9 (32%)	51 (35%)
Female	48 (65%)	29 (63%)	19 (68%)	95 (65%)
Marital status				
Married/cohabitation	17 (23%)	9 (20%)	8 (28%)	84 (58%)
Unmarried	57 (77%)	37 (80%)	20 (72%)	58 (40%)
Divorced	-	-	-	4 (2%)
Living arrangement				
Living with parents	18 (24%)	10 (22%)	8 (29%)	22 (15%)
Education				
No vocational education	27 (36%)	12 (26%)	15 (53%)	45 (31%)
Vocational school	34 (46%)	24 (52%)	10 (36%)	67 (46%)
Polytechnical university	10 (14%)	7 (15%)	3 (11%)	20 (14%)
University	3 (4%)	3 (7%)	-	14 (9%)
Employment status				
Employed	36 (49%)	23 (50%)	15 (54%)	87 (60%)
Student	14 (19%)	14 (30%)	9 (32%)	33 (23%)
Unemployed	4 (5%)	3 (7%)	2 (7%)	12 (8%)
Not student or unemployed	20 (27%)	6 (13%)	2 (7%)	14 (10%)
Treatment-related late effects (CTCAEv3)	(n=63)	(n=44)	(n=19)	-
No late effect	19 (30%)	7 (16%)	12 (63%)	-
Low-grade effect	21 (33%)	15 (34%)	6 (32%)	-
High-grade effect	23 (37%)	22 (50%)	1 (5%)	-

A total of 370 healthy controls with no chronic somatic disease selected randomly from the local population registry controlled by age, gender and living area were contacted by a letter. Only 2% (7), a total of 370, healthy controls wanted to attend the study at the department of pediatrics for a two-day late-effect study. However, 146 healthy controls (response rate 39.5%) filled in several

questionnaires, which were sent to them by mail. Ninety-five (65%) were female and 51 (35%) were male, and their mean ages were 26 and 24, respectively. There was no statistically significant difference in gender distribution, mean age or living area between the survivors and the controls. (II, III)

4.3 Measure

4.3.1 Neuropsychological Tests (I)

The neuropsychological tests were divided into four different groups according to what functions presumably were measured.

Intellectual functions. Seven subtests were selected from the complete test battery of the Wechsler Adult Intelligence Scale. The WAIS subtests used were Information, Comprehension, Similarities, Digit Span, Digit Symbol, Picture Completion, and Block Design. The verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) were estimated, and each subtest was also analyzed separately (Wechsler 1955).

Memory functions. Wechsler Memory Scale I was used (Wechsler 1945). In the Homogenous Interference Memory Test, the participants were asked to recall the first set of three isolated words that were presented in succession and then the second set. This was repeated three times with different words (Christensen 1975). The Verbal Learning Task included presenting the participants with a series of unrelated words, and then asking them to reproduce them in any order (Christensen 1975). In the Benton Visual Retention Test (BVTR), modified by Vilkki, the 10 cards of Form C were used, with the participant instructed to draw the figure(s) after the removal of the card (Vilkki 1989).

Orientation and attention. Trail-Making Tests A and B were used as previously described (Reitan 1971). The Stroop Color-Word Test consisted of instructing the participants to read aloud color words printed in black on the white card. After naming the colors the participants were asked to name the color of a circle. Finally, they were instructed to say the color of the written word, which was different from the color it names, without reading the words (Stroop 1935).

Motor performance. Instructions for the Purdue Pegboard Test were followed as previously reported (Lezak 1983). The Finger Tapping Test consisted of three 10-sec trials with the right and left hand separately (Lezak 1983). The Reaction Time Test required the use of a two-channel reaction time meter, where the

machine generates 200-msec light impulses at random interstimulus intervals (1–4 sec) on one or the other channel, left or right. The participants were instructed to push a button on the same side as the light was seen. The reaction time meter calculates means and variation rates of 10 light flashes (Winqvist *et al.* 2001).

4.3.2 Health related quality of life (HRQoL) (II)

We used the RAND-36 (Version 1.0) questionnaire to assess HRQoL. RAND-36 is an internationally used, validated and reliable self-report questionnaire for assessing HRQoL with Finnish population-based norms. The RAND-36 is composed of 36 items with standardized response choices and it contains eight different subscales: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP), and general health perception (GH). For each subscale scores were coded, summed up and transformed into a scale from 0 to 100, in which a higher score indicated better health (Aalto 1999).

4.3.3 Depressive symptoms and mental distress (III)

Beck Depression Inventory (BDI-21) was used with the aim of evaluating the depressive symptoms, and General Health Questionnaire (GHQ-12) to assess mental distress. These instruments are commonly used and meet the required standards for reliability and validity. (Beck *et al.* 1988; 1961, Daradkeh & Ghubash 2001, Goldberg *et al.* 1997, Holi & Marttunen 2003, Kilic *et al.* 1997, Pevalin 2000, Politi *et al.* 1994, Quek *et al.* 2001, Schmitz & Kruse 1999).

The BDI is a self-administered, 21-item instrument for evaluating depressive symptoms. Respondents rate symptoms on a four-point scale ranging from 0 to 3. Cut-off scores for clinically significant symptoms of depression are 10–16 (mild), 17–29 (moderate), and 30–63 (severe). A BDI score under four is suggested to indicate a denial or repression process in mental well-being and depression (Beck 1961).

The GHQ-12, a self-administered, twelve-item screening instrument for psychological distress, is also widely used and well validated. The scale measures recently experienced psychological symptoms, and each item is rated on a four-point scale with higher scores indicating higher mental distress. The scoring method in this study was bimodal (0, 0, 1, 1), i.e., the scores were calculated from

3 or 4 point answers only. The ideal cut-off sum value for identifying mental disorders varies between different studies, but the most commonly used cut-off sum value is >3, which was also used in our study. (Goldberg *et al.* 1997).

4.3.4 Physical late-effects and physical performance (II, IV)

Survivors were interviewed and examined by a pediatrician, and their medical files were reviewed. Diagnosed late effects were graded using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3). The CTCAEv3 represents the first comprehensive multimodality grading system to include both acute and late effects. CTCAEv3 grades adverse effects from 0 to 4. Grade 1 effects are minimal and usually asymptomatic. Grade 2 effects are moderate and they are usually symptomatic, but do not impair activities of daily living. Grade 3 effects are considered severe, requiring more serious interventions. Grade 4 effects are potentially life-threatening. Low-grade events (Grade 1 and 2) are considered tolerable and manageable. (Trotti *et al.* 2003).

The survivors underwent a physical performance test, which included the Pajulahti Sports Institute repeated movements test. The test included sit-ups (abdominal muscles), back extensions (dorsal muscles), crouches (muscles of the lower extremities) and push-ups (arm extensors). The test movements were repeated correctly as many times as possible during 30 seconds. The test results were classified as: 1 = Clearly below average, 2 = Below average, 3 = Average, 4 = Above average, 5 = Clearly above average. Respiratory and cardiovascular systems were tested with the UKK walking test. BMI was calculated from weight/square of height. (Keskinen *et al.* 2007).

4.3.5 The efficacy of the rehabilitation (IV)

The efficacy of the rehabilitation was evaluated at the end of the course by repeating the physical fitness tests and RAND-36 questionnaire. RAND 36 has been shown to be suitable for measuring the efficacy of rehabilitation. RAND 36 measured rehabilitees' HRQoL comprehensively and variedly. (Pekkonen 2010). Based on literature, a change of 3–5 units in the RAND-36 items is considered a minimally clinically important difference (MCID) (Hays and Morales 2001), which means that the changes observed can be considered clinically significant.

4.4 Statistical methods

Demographic variables were compared among the three groups using either the χ^2 test or analysis of variance, depending on whether the variables were categorical or continuous. To test differences between two groups, *t*-tests or Mann–Whitney *U*-tests were performed. Changes from one measurement to the next were computed, and paired *t*-tests were used to determine if the mean change differed significantly. All the statistical analyses were twotailed, and $P < 0.05$ was taken to indicate statistical significance. (I)

Differences between the groups were evaluated with *t*-test and variance analysis (ANOVA) with post-hoc Dunett analysis in continuous and normally distributed variables. Mann–Whitney *U*-test and Kruskal–Walls test were used with discrete and nominal variables. The one-sample *t*-test was used to compare the mean RAND scores of the study group with the mean scores of the Finnish control group. Categorical variables were analyzed using the Pearson Chi-Square test or Fisher’s exact test. A significance level of $P < 0.05$ was applied in all the analyses. All statistical analyses were performed using SPSS for Windows, version 14.0. (II)

The score differences in continuous variables between the groups were tested by using a Mann-Whitney *U*-test. The categorical variables were compared with a χ^2 test. All the statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) 16.0 for Windows. A significance level of .05 was used to describe statistically significant differences. (III)

The one-sample *t*-test was used to compare the mean RAND-36 scores of the study group with the mean scores of the Finnish control group. Efficacy of the rehabilitation was analyzed using a paired *t*-test. The score differences in continuous variables between the groups were tested by using Mann-Whitney *U*-test and Kruskal-Walls test with non-parametric variables. Categorical variables were analyzed using the Pearson Chi-Square test or Fisher’s exact test. A significance level of $P < 0.05$ was applied in all the analyses. All statistical analyses were performed using SPSS for Windows, version 14.0. (IV)

5 Results

5.1 Neuropsychological Tests (I)

IQ Test Scores

The irradiated ALL survivors had significantly lower test scores in VIQ ($P < 0.001$) and PIQ ($P < 0.001$) compared with the controls. The non-irradiated survivors also achieved significantly lower VIQ ($P = 0.006$) and PIQ ($P = 0.041$) scores compared with the controls. Among the irradiated survivors, all the subtest scores except the Comprehension subtest were significantly lower than the corresponding scores in the control group. Among the nonirradiated survivors, a statistically significant decline was observed in the Information, Digit Symbol and Similarities subtests compared with the controls (Table 4).

The verbal IQ (mean = 91, $P = 0.024$) and performance IQ (mean = 100, $P = 0.005$) scores of the irradiated survivors were significantly lower than those of the non-irradiated subjects (mean 100 and 111, respectively) (Table 4). All the subtest scores except for the scores in the Comprehension and Similarities subtests were found to be significantly lower among the irradiated survivors than among the non-irradiated survivors (Table 4).

No significant differences were found in VIQ or PIQ estimates among patients treated with a lower (18–23 Gy; VIQ mean 96, PIQ mean 100) or higher irradiation dose (24 Gy; VIQ mean 89, PIQ mean 100). However, the 11 patients with a relapse or BMT, who also received the most intensive treatments, had significantly lower VIQ and PIQ scores than the other ALL survivors (mean VIQ 83 vs. 96, $P = 0.004$, mean PIQ 94 vs. 106, $P = 0.018$, in the relapsed/BMT group and the other survivors, respectively). The VIQ scores of the relapsed/BMT group were also significantly lower when compared to the other irradiated survivors (83 vs. 94, $P = 0.016$), respectively. The difference in the PIQ scores was not statistically significant. It was remarkable that even nine out of 11 relapse/BMT patients had the VIQ scores below 85.

Memory Functions

The ALL survivors achieved significantly lower scores in all the memory tests than did the controls. The irradiated group achieved significantly lower test scores

in all the tests compared with the controls, whereas the mean scores of the non-irradiated survivors differed significantly from the controls only in Digit Span Forward ($P = 0.003$) (Table 4).

The irradiated survivor group performed all the memory subtests with lower test scores than did the non-irradiated group. The difference was significant in WMS Digit Span, WMS Immediate Logical Memory, WMS Delayed Logical Memory, Memory Interference Tests and the Verbal Learning Task (Table 4).

Orientation/Attention

The ALL survivors were significantly slower in the Stroop Color-Word and Trail-Making A ($P = 0.021$) and B ($P = 0.004$) tests compared with the controls (Table 4). The irradiated survivors were significantly ($P < 0.01$) slower in the Trail-Making A and B and the Stroop Color-Word Test than were the controls, whereas the non-irradiated survivors were significantly ($P < 0.05$) slower in the Stroop-Color-Word test compared with the controls. Additionally, the irradiated group performed significantly slower in the Trail-Making A ($P < 0.05$) and the Stroop Color-Word Test ($P < 0.05$) compared with the non-irradiated group.

Motor Performance Tests

Motor performance was found to be significantly slower ($P < 0.01$) in all the motor performance tests when compared with the controls. The non-irradiated group was significantly slower only in the Reaction Time Test ($P = 0.005$) compared with the controls. There was no statistically significant difference in motor performance between the irradiated and non-irradiated survivors (Table 4).

Table 4. Results of the neuropsychological tests among irradiated and non-irradiated young adult survivors of childhood acute lymphoblastic leukaemia (ALL) and healthy controls.

Variable	Irradiated Survivors (n=44)			Non-irradiated Survivors (n=20)			Controls (n=45)		
	M	Range	p ^a	M	Range	p ^a	M	Range	p ^a
VIQ	91	(65-123)	.024	100	(65-120)	.006	109	(80-127)	.000
Information	9	(4-15)	.017	11	(3-16)	.044	13	(7-18)	.000
Comprehension	9	(4-12)	.393	9	(3-12)	.747	9	(5-13)	.120
Similarities	8	(3-14)	.226	9	(3-14)	.000	13	(10-17)	.000
Digit Span	8	(3-19)	.026	11	(7-18)	.011	13	(7-15)	.000
PIQ	100	(62-145)	.005	111	(85-141)	.041	118	(95-150)	.000
Picture Completion	10	(3-16)	.068	11	(5-16)	.171	12	(9-17)	.000
Block Design	10	(5-15)	.001	12	(6-17)	.579	13	(7-19)	.000
Digit Symbol	11	(4-19)	.029	12	(7-18)	.242	13	(7-15)	.000
Memory functions									
WMS Number Series Forward	6	(0-8)	.187	6	(4-8)	.003	7	(5-8)	.000
WMS Number Series Backwards	4	(2-7)	.019	5	(3-7)	.382	5	(3-7)	.000
WMS Immediate Logical Memory	10	(1-18)	.006	13	(2-20)	.711	14	(9-20)	.000
WMS Delayed Logical Memory	9	(1-16)	.007	12	(2-19)	.824	12	(9-15)	.000
Memory Interference	13	(8-18)	.017	15	(7-18)	.426	16	(9-23)	.000
Verbal Learning Task	40	(26-50)	.025	44	(32-48)	.051	45	(37-49)	.000
Benton-C	22	(14-26)	.021	24	(18-26)	.892	24	(20-26)	.022
Orientation and attention									
Trail-Making test A	31	(16-51)	.023	27	(11-42)	.820	27	(20-39)	.001
Trail-Making test B	89	(35-281)	.115	72	(23-164)	.095	60	(28-127)	.001
Stroop Color-Word	115	(80-207)	.028	102	(78-138)	.025	91.9	(65-130)	.000
Motor functions									
Purdue Pegboard. Right hand	15	(7-19)	.051	16	(12-19)	.549	16	(14-19)	.003
Purdue Pegboard. Both hands	12	(7-16)	.063	13	(9-19)	.914	13	(12-18)	.007
Reaction Time	370	(224-776)	.465	353	(264-460)	.005	313	(214-461)	.001
Finger Tapping. Right Hand	48	(32-65)	.064	52	(39-65)	.431	53	(41-64)	.000
Finger Tapping. Left Hand	44	(31-59)	.132	47	(37-57)	.239	49	(39-60)	.000

VIQ Verbal Intelligence Quotient (Wechsler Adult Intelligence standard test score); PIQ Performance Intelligence Quotient (Wechsler Adult Intelligence standard test score). P^a difference between irradiated and non-irradiated groups; P^b difference between non-irradiated and control groups; P^c difference between irradiated and control groups.

5.1.1 Comparison of IQ at the end of Treatment, 5 Years After Treatment and a Mean of 17 Years After Completion of Therapy

A total of 45 survivors had results of a previous neuropsychological testing available. Figures 2 and 3 show the mean verbal and performance IQ of the survivors in the irradiated and the non-irradiated groups at three different time points. Significant decline during the study period was observed both in VIQ and PIQ in the irradiated group, but only in VIQ in the non-irradiated group (Figs. 2 and 3).

Irradiated Group

In the paired t-test analysis the mean decline in VIQ among the 16 irradiated survivors was 7 (95% CI 3–10) standard points and in PIQ 12 (95% CI 5–18) standard points between the first and the last examination. The decline in VIQ between the second and the last examination among the 20 irradiated survivors was a mean of 5 (95% CI 1–10) and in PIQ 8 (95% CI 3–12) standard points.

Non-Irradiated Survivors

In the paired t-test analysis the non-irradiated survivor group showed a significant decline in VIQ between the first and the last examination, mean 8 (95% CI 2–13) standard points (N = 12). Instead, no significant decline was seen in PIQ, mean change 3 (95% CI –4–9) standard points. No significant IQ changes were observed between the second and the third examination in this group.

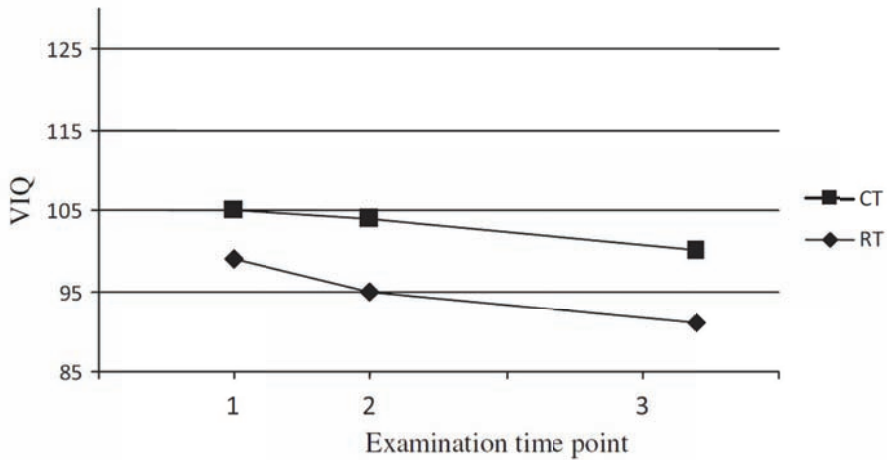


Fig. 2. Mean VIQ scores at the end of leukaemia treatment (1), 5 years later (2), and a mean of 17 years after completion of the therapy (3) in survivors treated with radiation therapy (RT) and with chemotherapy only (CT). In the RT group a statistically significant decline was found between the first and the last examination ($P = 0.007$) and between the second and the last examination ($P = 0.0017$). In the CT group a significant decline was observed only between the first and the last examination ($P = 0.032$).

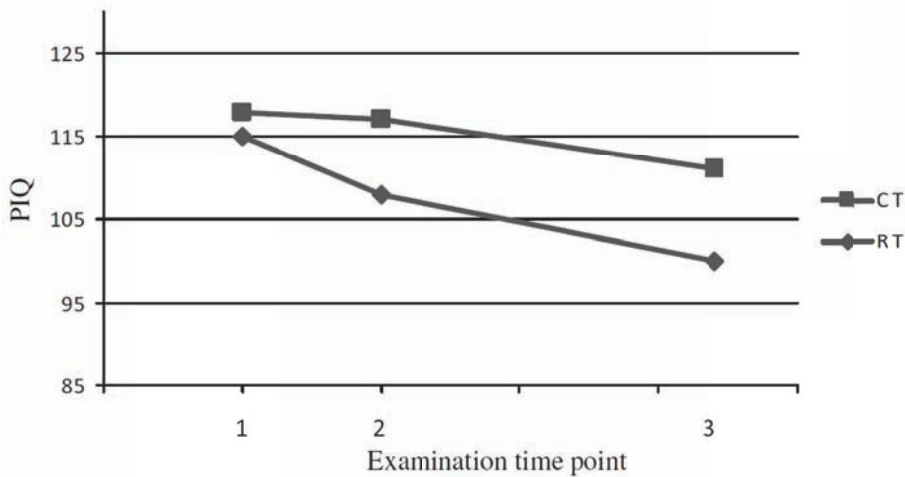


Fig. 3. Mean PIQ scores at the end of leukaemia treatment (1), 5 years later (2), and a mean of 17 years after completion of the therapy (3) in survivors treated with radiation therapy (RT) and with chemotherapy only (CT). In the RT group a statistically significant decline was observed between the first and the last examination ($P = 0.005$).

and the second and the last examination ($P = 0.005$). In the CT group the difference was not statistically significant.

5.2 HRQoL

5.2.1 Physical late-effects

Expert rating showed that treatment-related low-grade (mild or moderate) late effects were present in 33% and high-grade (sever or life threatening) effects in 36% of the ALL survivors. Lifethreatening late effects were diagnosed in 17% of the irradiated survivors. Severe late effects included infertility (seven cases), epilepsy (two cases), cognitive impairment (one case), obesity (four cases) bone exostosis (one case) and hearing loss (one case). Lifethreatening late effects were found in 11 survivors (13 secondary malignancies and 1 epilepsy). Compared to the controls, the survivors were less often married and lived more often with their parents (Table 3).

5.2.2 Emotional and social well-being

BDI scores indicated moderate or severe depression significantly less frequently in the ALL survivors compared to the controls (1.4% vs. 8.9%, $p = 0.039$). BDI scores indicated no depression in 80.8% of the ALL survivors and 73.3% of the control group.

In the GHQ, 80.8% of the ALL survivors and 78.8% of the control group reported no mental distress. The mean GHQ scores were under the cut-off score in both of the groups, and the scores did not differ significantly between the groups.

Exploration of the depressive symptoms revealed that the ALL survivors obtained significantly lower mean BDI scores compared with the controls, indicating fewer depressive symptoms. Treatment group had no effect on the BDI scores: no significant difference was found between the irradiated and non-irradiated treatment groups. However, the irradiated ALL survivor group obtained a significantly lower mean score than the control group. No significant difference in BDI scores was found between the non-irradiated survivors and the controls.

In comparison to the controls, survivors with equal or more than 20 years of follow-up had significantly lower scores in BDI than controls ($p = 0.010$). There

were no group differences between survivors with 20 or more years of follow-up and the survivors with shorter follow-up.

Contrary to our expectations, no significant differences in BDI scores were found between genders among the ALL survivors. However, the female survivors obtained significantly lower BDI scores than the female control group (2.77 vs. 7.13, $p < 0.05$). The BDI scores of the irradiated survivors did not differ significantly from the non-irradiated survivors or the control (2.96 vs 3.38), but the irradiated females obtained significantly lower mean BDI scores than did the female controls (2.50 vs. 7.13, $p < 0.05$). No significant differences were observed between nonirradiated survivor males or females when compared with the controls.

Survivors with high-grade (severe or life-threatening) late-effects did not differ statistically in BDI (3.34 vs 5.67), or GHQ-12 scores from the healthy controls (1.29 vs 1.64), or from those with no or low-grade late-effects (BDI 3.43 vs 2.74; GHQ 1.29 vs 1.06). However, mean BDI scores in 11 ALL survivors with life-threatening late effects were remarkably lower than in the control group (mean 1.2 (SD 2.1) vs. 5.7 (SD 9.0)), although the difference did not reach statistical significance.

5.2.3 HRQoL in ALL survivors after an average of 20 years after the diagnosis

Comparison with the Finnish population norms showed that the ALL survivors scored statistically significantly better than the average in all dimensions of RAND-36 except for the bodily pain subscale. The HRQoL was better than the norms in both the irradiated and non-irradiated groups in six subscales.

ALL survivors showed good HRQoL scores in comparison to the healthy young adults selected randomly from local population registry (control group). They scored significantly better than controls on the subscales of role limitations due to emotional problems ($P = 0.030$), mental health ($P = 0.030$), and vitality ($P = 0.004$). There was no difference between survivors and the control group in the subscale general health. The irradiated group had significantly higher scores on the subscales of mental health ($P = 0.027$) and vitality ($P = 0.009$) compared to controls.

There were no group differences between irradiated and non-irradiated survivors, or between irradiated male and non-irradiated male survivors. However, compared to female controls, female survivors had significantly higher scores on

role limitations due to emotional problems ($P = 0.005$), vitality ($P = 0.004$), mental health ($P = 0.002$), social functioning ($P = 0.040$), and bodily pain ($P = 0.016$).

In comparison to the controls, survivors with more than 20 years of follow-up had significantly higher scores in vitality ($P = 0.006$) and mental health ($P = 0.011$). Furthermore, on the subscale vitality ($P=0.043$) and mental health ($P = 0.040$), survivors with highgrade late effects scored significantly better than controls. Relapsed survivors obtained significantly better scores on the subscales mental health ($P = 0.004$) and vitality ($P = 0.004$) than the controls (Table 5).

Table 5. The score differences for RAND-36 dimensions among of low- and high-grade late- effects, relapse and controls. Out of the 74 participants altogether 63 participated to the medical examination, of which 19 had no medical late-effects. An asterisk denotes statistically significant difference against the control group (* $p < .05$, ** $p < .001$, * $p < .001$).**

RAND-36	Low-grade effect (n=21)		High-grade effect (n=21)		Relaps (n=11)		Controls (n=146)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physical functioning (PF)	92	17	93	9	93	9	95	10
Role limitations due to physical problems (RP)	70	40	89	25	91	20	84	28
Role limitations due to emotional problems (RE)	89	26	84	32	82	31	82	31
Vitality (VT)	72	12	78*	16	83**	11	68	19
Mental health (MH)	79	14	82*	19	85**	21	75	18
General health (GH)	69	25	76	21	76	27	74	18
Social functioning (SF)	84	21	91	17	92	19	87	20
Bodily pain (BP)	74	26	85	19	85	23	79	22

5.2.4 The occupational rehabilitation course

Despite the overall high scores in RAND-36, need for rehabilitation was observed in 14 survivors by the examiners and the expert group. Altogether, nine subjects participated in a rehabilitation course. There was no significant difference in the RAND-36 scores between those who were selected to the rehabilitation course compared to the scores of the non-participant group.

Treatment-related severe or life threatening late effects were found by expert rating in as many as 67% of the participants. Severe late effects included secondary malignancies, complete infertility, cognitive impairment and

hypopituitarism with growth impairment and one case with multiple bone exostosis. In addition to these, survivors had impaired hearing/ unilateral deafness, musculoskeletal symptoms, obesity, allergy, asthma, head ache, insomnia, depression and drinking problem.

At the onset of rehabilitation, participants' physical functioning was somewhat/clearly poorer than average in all domains. Over the course of rehabilitation, physical functioning improved, but remained somewhat below average. BMI decreased to normal during the rehabilitation period.

The course participants reported good HRQoL measured by RAND-36 Comparison with the Finnish population norms showed that they scored statistically even better on the subscales physical functioning ($p = 0.024$), role limitations due to emotional problems ($p = 0.000$) and social functioning ($p = 0.006$). There was no difference between the survivors who participated in the rehabilitation course and those who did not.

These young adult survivors of childhood ALL reported good mental well-being and no depressive symptoms. There was no difference between those ALL survivors who participated in the rehabilitation course and who did not.

Following rehabilitation, a negative change was seen in six domains of HRQoL. This change was not statistically significant. At the beginning of rehabilitation, the survivors who participated in rehabilitation scored statistically even better on the subscales physical functioning ($p = 0.024$), role limitations due to emotional problems ($p = 0.000$) and social functioning ($p = 0.006$), but this difference was no longer seen at the end of the rehabilitation period.

Nearly half of the young participants had some indication of a mood problem, which not all of them were able to recognise or willing to address. Some brought up depressed mood, which had in some participants been associated with suicidal ideation. The rehabilitees also brought up problems associated with adaptation and self-esteem. In addition, some had problems with alcohol use, which they denied, however.

Further measures and recommendations

Disability pension was recommended for one of the participants. One of them was recommended work practice via the Social Insurance Institution/Farmers' Social Insurance Institution at another place of work in order to assess work ability. One of the participants was accepted to a study program; the onset of studies was postponed for a year because she had a job she liked. One of the participants went

abroad to work and take part in a course. One had a job interview lined up at the end of the course. Four course participants continued to look for work. They were deemed not to be in need of vocational training; their problem with finding a job was due to their psychosocial situation and lack of motivation. They were still in need of special support. (Table 6).

The rehabilitees' job/study situation one year and five years after rehabilitation

After a one-year follow-up, the rehabilitees' life situation had not changed significantly compared to the final phase of the rehabilitation. Three were employed, four were still looking for a job, and one was studying. One of the rehabilitees had been granted a pension. At the one-year follow-up, the rehabilitees were also asked to assess how issues associated with key matters had been addressed during the course in relation to their needs. Two survivors thought that there had not been enough emphasis on job-related issues. They were dissatisfied with how they had been able to find employment. Partly for this reason, they felt that the vocational intervention had been useless. Five years after the end of the rehabilitation course three of the participants were on retirement, four were employed, and one had died. One person was lost to follow-up. Three out of four employed survivors had changed to a less demanding job. (Table 6).

Table 6. The rehabilitees' characteristics and job/study situation one year and five years after rehabilitation.

Participant	Age when diagnosed	Age when rehabilitation	Treatment	Gy Relaps	CVCA	Cognitive/ Learning difficulties	Education	Marital status	Work experience	Futher recommendations	Clarifying of the occupational situation	Physical and psychosocial limitation	Situation after rehabilitation after 1 year	Situation after 5 years
1	7	28	Radiation	24	Severe	Yes	no vocational	Unmarried with parents	1	Disability pension	Yes	Yes	Retired	Retired
2	6	20	Radiation	24	Mild	No	Vocational	Unmarried		Education	Yes	No	Student	Lost follow up
3	3	21	Non radiation	No	Mild	No	no vocational	Married	0,5	Education	Yes	No	Employed	Student employed
4	3	32	Radiation	25	Life-threatening	Yes	Vocational	Unmarried	4	Work/Education	No	Yes	Work applicant	Retired
5	14	31	Radiation	30	Moderate	Yes	Vocational	Unmarried	5	Therapy and education	No	Yes	Work applicant	Deceased
6	3	30	Radiation	21	Severe	Yes	no vocational	Unmarried with parents	6	Work practice	No	Yes	Employed	Employed
7	2	34	Radiation	24	Life-threatening	Yes	Vocational	Unmarried with parents	3,5	Work	No	Yes	Work applicant	Employed
8	1	25	Radiation	21	Mild	Yes	Vocational	Married/ 2 child	4	Work/Updating education	Yes	Yes	Work applicant	Employed
9	4	33	Radiation	25	Life-threatening	No	Vocational	Divorced (cohabiting)	3	Updating education	No	Yes	Work applicant	Retired

6 Discussion

6.1 Discussion on results

6.1.1 Neuropsychological functioning

In this study we found that young adult survivors of childhood ALL treated with cranial irradiation had clear progressive deficits in their neurocognitive functioning at a mean of 20 years after diagnosis compared with healthy controls. Statistically significantly lower test scores were found in verbal and performance IQ, memory functions, orientation/attention and motor functions. Non-irradiated ALL survivors performed significantly better, but even they had statistically significant impairments in some of the neuropsychological test scores compared with the controls, particularly in the areas of VIQ and PIQ, sequential reasoning, working memory and information processing speed.

These findings are consistent with most other studies that demonstrate major cognitive impairment of CRT and milder deficits among those treated with chemotherapy only. Since the first report by Meadows *et al.* (1981) numerous studies have shown that cancer patients treated with irradiation are at the greatest risk of developing treatment-related neurocognitive deficits. A recent meta-analytic review of the neurocognitive effects of CRT reported decreased intellectual functioning, poor academic achievement, deficient attention, information processing, executive functioning, psychomotor and visuospatial skills, and memory compared with controls (Campbell *et al.* 2007). However, somewhat controversial results have been obtained concerning late effects of chemotherapy only. The most common neuropsychological effects of chemotherapy alone involve deficits in visual processing (Brown *et al.* 1998, Copeland *et al.* 1996), visual-motor functioning (Copeland *et al.* 1996, Kingma *et al.* 2002, Mahone *et al.* 2007) and attention and executive functioning (Buizer *et al.* 2009, Espy *et al.* 2001, Moleski 2002, Waber 2000). The results of this study agree well with studies, which have shown that chemotherapy without irradiation of the central nervous system might decrease cognitive and academic functioning (Copeland *et al.* 1996, Moleski 2000, Peterson *et al.* 2008). Mennes *et al.* (2005) concluded that children treated for ALL with chemotherapy are impaired only in selective aspects of cognitive functioning; attention, concentration and information processing speed. Memory difficulties are multifactorial in origin.

Inefficient storage of new information can be compounded by diminished attention and poor information-processing skills. (Brouwers & Poplack 1990, Mirsky *et al.* 1991, Rodgers *et al.* 1992). In our study attention tests were performed with lower test scores by irradiated survivors. Even non-irradiated had difficulties in the Digit Span subtest. Attention and concentration impairments are particularly common for ALL survivors (Langer *et al.* 2002, Mulhern & Butler 2004, Rodgers *et al.* 1999, Nathan *et al.* 2007, Rodgers *et al.* 2003). In our study the irradiated survivors performed slower in motor performance tests when compared with the control group, and this is one of the most frequently documented findings also in other ALL studies (Moleski 2000). However, the non-irradiated group had deficits only in their reaction times, and this finding is in accordance with the results reported by Mennes *et al.* (2005).

Our findings of progressive decline after cranial irradiation therapy is supported by Kato *et al.* (1993) who also observed IQs decline even 10 years after diagnosis. Link *et al.* (2006) investigated 44 adults treated for childhood ALL, and showed impaired neuropsychological capacity in the period 8–27 years after CRT. Despite methodological shortcomings, we also had evidence of a decline in cognitive functioning even in non-irradiated survivors.

The decline in cognitive performance among the ALL survivors of this study could be explained by white matter changes in the brain. White matter appears to play an important role in neurocognitive problems (Cole & Kamen 2006, Moore 2005) and even a slight pathology of white matter has been associated with brain dysfunction (Cole & Kamen 2006, Reddick *et al.* 2006). Reddick *et al.* (2006) find that smaller white-matter volumes were associated with larger deficits in attention, intelligence, and academic achievement. Survivors who received cranial irradiation had more severe impairment of white-matter volume development and more significant deficits in learning, instead survivors who received chemotherapy alone had less damage to the white matter and were able to compensate intellectually and academically for attentional deficits. (Reddick *et al.* 2006). Researchers have hypothesized that the developing brain may be more susceptible to damage, because newly synthesized myelin has higher metabolic activity and lower stability that makes it more vulnerable to the toxic effects of therapy (Anderson *et al.* 2009). This assumption is also supported by the finding of recent magnetic resonance imaging studies (Anderson *et al.* 2009, Lesnik *et al.* 1998, Mahone *et al.* 2007). White matter abnormalities in aging have also been associated with cognitive decline that leads to dementia. Our relapsed/BMT survivors had below normal IQ scores. They had received also the highest doses

of CRT and neurotoxic chemotherapy. It remains to be seen whether additional white matter loss with aging places these survivors at increased risk of early dementia later on in their lives.

6.1.2 Depressive symptoms, well-being and health-related quality of life

Compared to healthy controls, ALL survivors reported significantly less depressive symptoms or depression in BDI and an equal amount of mental distress in GHQ-12. In this study, the irradiated and female ALL survivors reported less depression than the other study groups.

It is difficult to draw firm conclusions of the prevalence of depression in adult survivors of childhood leukaemia from the published articles, but generally most survivors seem not to be particularly depressed (Marsland *et al.* 2006, McDougall & Tsonis 2009). Supporting our findings, in a report from the Childhood Cancer Survivor Study Zelzer *et al.* (2008) and others found that the survivors had lower scores for depression, anxiety and global distress compared to the population norms. Likewise Pemberger *et al.* (2005) found less depression in a group of 78 childhood cancer survivors than the population norms using the same BDI questionnaire as was used in this study. Large scale multi-centre studies suggest that the young adult survivors may be at slightly greater risk of depressive symptoms compared to siblings (Pemberger 2005, Zeltzer *et al.* 1997). In a large, sibling-controlled study of young adult survivors of childhood leukaemia, Hodgkin's disease, and non-Hodgkin's lymphoma, Zebrack *et al.* (2002b) found that survivors had a significantly increased risk for reporting symptoms of depression and somatic distress, but the rates fell within the population norms. Using parental reports, Schultz *et al.* (2007) found the risk for symptoms of depression, anxiety and psychological problems to be 1.5 times higher in adolescent survivors of childhood cancer compared to their siblings.

We found that young adult survivors of childhood ALL reported good HRQoL. The survivors even had significantly higher scores than controls on the subscales role limitations due to emotional problems, mental health and vitality. Long follow-up time, more severe late effects and treatment for a relapse were associated with higher quality of life, especially in the dimensions of vitality and mental health. No difference was found on the general health subscale between the study groups. However, treatment-related late effects were found by expert rating in 70% and severe late effects in as many as 36.5% of the survivors.

Chronic health conditions have been associated with a reduced QOL. Nevertheless, in our study the survivors who had been diagnosed more than 20 years ago and who had high-grade late effects of treatment or had even relapsed had higher scores than other survivors or controls. However, our results are congruent with previous findings that seven out of 10 survivors develop at least one medical late effect, which can include the development of physical impairments and second malignancies (Oeffinger *et al.* 2006). The frequency of life-threatening late effects was as high as 17% in the irradiated group, possibly explained by a high rate of secondary malignancies, mainly meningiomas in our study population (Banerjee *et al.* 2009). They were also less often married and more often living with their parents compared to the controls.

Our findings that ALL survivors rated their general health and social functioning as good are in discordance with the magnitude of the detected late-effects. The findings of the current study are in accordance with the results of other studies where the survivors of cancer had equal or better HRQoL than controls or population norms (Apajasalo *et al.* 1996, Blaauwbroek *et al.* 2007, Elkin *et al.* 1997, Langeveld *et al.* 2004;2002, Pemberger *et al.* 2005, Zebrack & Zeltzer 2003). In contrast to our study, a recent study by Blaauwbroek *et al.* (2007) found lower HRQoL in adult very longterm childhood cancer survivors than in survivors diagnosed more recently. This discrepancy between the results of our study and that of Blaauwbroek *et al.* (2007) may be explained by the inclusion of only survivors of leukemia in our study. Several studies have examined the HRQoL among the ALL survivors with more or less conflicting results, which may be at least partly due to methodological differences. Zeltzer *et al.* (2008) found that survivors had poorer outcomes on six out of eight dimensions in SF-36. Mody *et al.* (2008) found in a large study that ALL survivors reported more adverse general health and mental health, functional impairments, and activity limitations compared with their siblings. Further, survivors who had received irradiation or had suffered a relapse were found to have the greatest risk for lower HRQoL, which is in contrast to our findings. Mody *et al.* 2008). Meeske *et al.* (2005) found that survivors without fatigue had significantly higher QOL in five out of ten SF-36 subscores compared to population norms. Most interestingly, significantly higher scores than in the present study were found on the same subscales of vitality, mental health and role limitations due to emotional problems (Meeske *et al.* 2005). However, in the study of Meeske *et al.* (2005) survivors who suffered from fatigue had lower QOL than population norms. Unfortunately, we did not measure fatigue separately among our survivors.

6.1.3 The occupational rehabilitation intervention

We aimed to investigate here whether occupational rehabilitation could improve employment and quality of life in survivors of ALL with reduced ability to become employed. In our study the employment of the survivors did not improve significantly. Five years after the rehabilitation course one of the nine participants had died, three were entitled to permanent disability retirement and four were employed. Three of them had changed to less demanding work. The physical fitness of the survivors improved and their BMI decreased after rehabilitation. Instead HRQoL declined in 6 out of 8 domains.

In contrast to our study, earlier studies have reported higher rate of employment after institutional occupational rehabilitation in various disease groups in Finland (Järvikoski 2002). In our study, the problems of employment persisted almost invariably after rehabilitation. One third of the participants were on disability pension after a five-year follow-up period. This may be explained by poor selection of participants. Vast majority of participants of rehabilitation here had advanced functional and occupational deficits related to the leukemia experience and treatment, which significantly reduced the potential for occupational rehabilitation. Many of these survivors had undergone several attempts of vocational rehabilitation before participation in this study. For some of the survivors here a goal of becoming employed was too high. Correct targeting and timing of the intervention plays a key role for finding employment (e.g. Pohjola 2006), since institutional rehabilitation benefits neither healthy nor too ill individuals (Pekkonen 2010).

In our study measuring HRQoL by RAND-36 was neither useful in identifying participants with occupational problems nor in measuring the effect of rehabilitation. We observed a surprising shift in a negative direction in six domains of HRQoL during the follow-up. Despite of significant improvement in physical fitness and decrease in BMI, scores of physical functioning in RAND-36 decreased to the level of normal population scores. This discrepancy may be an indicator of more realistic self image and better awareness of physical deficits and hinders of employment. In our previous study we have shown that RAND-36 is not an appropriate instrument for measuring HRQoL in this group of survivors (Harila *et al.* 2010).

6.2 General discussion

Childhood cancer can be a devastating experience that places patients at increased risk for disruption in psychological functioning (Zebrack 2000). A life-threatening disease does not necessarily lead to long-term impairment of mental well-being, but may even generate positive effects. It can lead to greater emotional maturity and finding a new outlook on life. (Marsland *et al.* 2006, Phipps 2005). As Andrykowski *et al.* (1993) suggested a serious illness should not be viewed as a stressor with only negative outcomes, but rather as a transitional event which creates opportunity for both positive and negative outcomes.

As the disease is treated in childhood, survivors' development of coping strategies may be affected in such a way that the subjects tend to repress possible difficulties in their lives and overestimate their well-being -“ disability paradox”. The results could possibly be explained by denial mechanism of the long-term cancer survivors compensating and overcompensating extant late effects. (Canning *et al.* 1992). Repressive adaptive style has been documented among cancer patients in childhood and adolescence (Canning *et al.* 1992, Gil 2005), but the adaptive styles have been poorly studied in long-term survivors. Repression in previous studies has been characterized by under-reporting the negative aspects in self-administered questionnaires and by emphasizing the positive elements.

We believe that our finding of fewer depressive symptoms in the BDI than the controls and, the mean BDI score in the ALL survivors group was below four, indicating denial or repression of negative thoughts and emotions. Findings of higher HRQoL in more affected ALL survivors lends support to the idea of socially desirable response bias (SDRB). Also findings of declined HRQoL after rehabilitation support idea of response shift. Studies suggest that response shift is found in cancer patients, but no consensus has been reached on the magnitude and direction of the shift. In our study irradiated survivors were the oldest, treated during the early era when supportive care and psychosocial support were not at the level where they are today, which may have contributed to the development of SDRB. More recently treated survivors who had very few, if any, late effects did not differ from their healthy peers, which seems to indicate that they have coped well with the childhood trauma.

Socially desirable response bias (SDRB) has recently been reported to affect the assessment of subjective quality of life among childhood cancer survivors. The results of this study also refer to the notion that the repressive adaptive style may persist into adulthood among the ALL survivors, or on the other hand, that

psychological distress may manifest itself as bodily pain. The SDRB is thought to be a gradually developing unconscious process to cope with stressful life situations, leading the subjects to underreport negative aspects in their lives and accentuate positive. It is reasonable to consider cancer as a very stressful illness. As the disease is treated in childhood, the survivors' developing coping strategies may be affected in a way that the subjects tend to deny possible difficulties in their lives and overestimate their well-being. (O'Leary *et al.* 2007).

The idea of SDRB leads further to the issue that it would be important to assess the defensive styles and coping mechanisms of the patients in order to obtain a reliable picture of the true quality of life. Quantitative methods suffer from limitations in this, but with qualitative methods they may be easier to achieve. These two approaches support each other, and should by no means be considered as excluding each other. One should keep in mind that HRQoL cannot be considered as a single entity; rather, it should be seen as consisting of several dimensions. These dimensions are investigated with several methods, which the conflicting results of the previous studies possibly refer to. Drawing general assumptions about the true quality of life is therefore difficult to accomplish. This accounts for the idea of calculating the mean scores at group level, which inevitably leads to loss of individual information.

Further, at the individual level, HRQoL is affected by a multiple number of uncontrollable variables, which in turn very likely affect the subjective meanings. Attempts to estimate the quality of life with self-rated questionnaires is thus difficult; this is important, considering that the assessment of HRQoL is often accomplished as part of treatment or rehabilitation plans. Correct targeting and timing of the occupational rehabilitation intervention plays a key role for finding employment (e.g. Pohjolainen 2006). If we can determine factors that complicate ALL survivors in finding employment, we may be able to help them to prepare for the labor market.

6.3 Methodological considerations

6.3.1 Strengths and weaknesses of the study

The strength of this study is that it has one of the longest follow-ups (20 years) of ALL survivors with representative data, and it is one of the first studies with a vocational training intervention aimed at ALL survivors. The present study was

based on an extensive neuropsychological test, well-known measures of the HRQoL dimensions and depressive symptoms. Also late effects were graded using CTCAEv3.

The strength of our neuropsychological study is the long follow-up period and inclusion of longitudinal comparison data. The patients were personally and carefully interviewed and examined by a pediatrician and a psychologist. Although heterogenic, we believe that the studied group represents quite well the first cohort of survivors. We also included a healthy control group in our study. Unfortunately we did not have any follow-up data of the controls available.

One limitation of this study is the relatively small group of participants, which also included relapsed patients. The survivors had been treated with various treatment protocols, and the fact that SDRB or a coping mechanism was not assessed. The present study also suffers from limitations in assessment of the other variables possibly influencing HRQoL aside from the diagnosis and treatments or sociodemographic variables. We also had a control group, randomly recruited from the general population. Their response rate was low (40%), which raises the question of selection bias. However, comparisons against the Finnish population normative scores were conducted in RAND-36. The rehabilitation data set is small, comprising only a study group, which puts considerable limitations on interpretation of results. The specific impact of rehabilitation cannot be evaluated with this study design due to lack of a control group. Selection of participants for rehabilitation was not successful, because many of them did not have preconditions for employment. This group may have benefited from different type of rehabilitation e.g. rehabilitation focusing more on psychosocial well-being.

Measuring HRQoL is today an important outcome indicator in evaluating health-care interventions. It has been stated that HRQoL should be included in all randomized cancer trials in addition to other outcome measures (Eiser 2004, Pickard 2004, Solans 2008). However, the concept of HRQoL is inexact and thus difficult to measure. A large number of instruments have been developed, including both generic and disease-specific measures. (Wiebe 2003). The former are designed to capture all aspects of HRQoL, and are used to collect information on healthy as well as ill individuals. Disease-specific instruments, on the other hand, aim to collect information on disease-specific health problems from more specific populations. Disease-specific instruments tend to be more sensitive to treatment-related changes, although the generic instruments provide a broader context about change in HRQoL. (Wiebe 2003). Although the majority of the

instruments meet accepted standards of internal consistency and validity, relatively few provide data on test-retest reliability, structural validity, and sensitivity to change (Wiebe 2003). Large numbers of studies have even used non-standardized, study-specific instruments, which does not allow cross-study comparisons. Relative responsiveness varies across patient populations, which also partially explained our findings in the most affected leukemia survivors.

These quantitative questionnaire-based methods are an easy and cheap way to measure HRQoL in large groups of individuals and thus attractive. This has resulted in a large number of research articles in cancer patients and survivors, and the results have been contradictory. Our study results lie at the most positive end. The results from other investigations and personal contact with the survivors revealed that RAND-36 did not measure the true HRQoL, especially in the survivors with the most severe adverse effects of treatment. In previous studies with positive HRQoL findings in cancer survivors the result has been accepted as an indicator of positive psychological growth and change of values after a life-threatening disease without taking into account the possibility of response bias (Stam 2001, Zeltzer *et al.* 2009). At least according to our findings, HRQoL questionnaires may not be an appropriate way to measure the effectiveness of rehabilitation, either.

In addition to problems with poor measurement instruments, the majority of quality of life studies have also suffered from other methodological weaknesses, which include differing definitions and operationalization of the concept of HRQoL from one study to another, small sample sizes and low participation rates.

Problems of measuring QOL make evaluation and comparison of QOL difficult. QOL research presents an ethical dilemma: how to deal with an individual's adaptation to lower achievement level and subjective satisfaction in a situation which objectively appears unsatisfactory? Should satisfaction of the survivors lead to withholding of rehabilitation or other interventions aiming to improve their situation? Survivors have individual needs, which can best be fulfilled if they are followed by health care professionals that are well aware of the consequences of cancer treatments. In many countries special late-effect clinics have been established. Such clinics would also improve the situation of our survivors in Finland, especially for those who have received the most harmful and intensive cancer treatments, e.g. cranial irradiation.

6.3.2 Future perspectives

We conclude that long-term survivors of ALL rate their HRQoL as good. However, we agree with O'Leary *et al.* (2007) that self-reported health-related quality of life has to be interpreted with caution. We suggest that high scores of quality of life measured with self-reported questionnaires cannot be trusted blindly; it would be more important to find out what these scores tell us. It appears that self-reported inventory may not be an optimal tool in assessing HRQoL among ALL survivors. Referring to the previous incongruent results and the results of this study, it seems that in addition to quantitative approaches also qualitative dimensions are needed in assessment of HRQoL to gain more specific individual information about the subjects' quality of life.

In future, studies on HRQoL in childhood cancer survivors should consider synthesizing generic and cancer-specific measures and including qualitative measures especially when looking at coping mechanisms. In order to understand the whole picture of cancer survivors' QoL, also "hard data" on adverse late effects should be included. One option to improve the QoL measurement is to add proxy reports in the studies. Comparisons of qualitative and quantitative data would provide a more comprehensive understanding of the survivors' experiences and document the personal relevance of the different aspects of survivors' HRQoL measures for individual survivors. Comparisons of group means on a variety of measures can give the impression that adjustment does not change over time, while inspection of individual scores can show a completely different pattern. Comparisons with norms can reveal that the population has a specific problem, but tell us nothing about the processes whereby the problems arose. Attention also needs to be given to issues of clinical rather than statistical change.

It would also be valuable to include the assessment of the defensive styles and coping mechanisms and response shift of the survivors. In the light of the results of the present study, which indicate that the subjects who presumably should have the lowest HRQoL do in fact report the greatest well-being, this use of qualitative measures seems to be especially important in the case of survivors with the most severe treatment-related late-effects.

In the future we should identify the need for occupational rehabilitation earlier, and aim at developing selection criteria that identify those who can be expected to benefit from such an intervention.

7 Conclusions

Survivors of childhood ALL suffer from long-lasting progressive neuropsychological impairment, especially when treatment includes cranial irradiation.

Survivors of acute lymphoblastic leukaemia report fewer depressive symptoms and equal mental well-being compared to healthy controls. Our findings support the idea that childhood leukaemia survivors' subjective experience of well-being is possibly affected by repressive adaptive style.

Long-term survivors of childhood ALL reported equal or better HRQoL in RAND-36. Higher HRQoL scores were associated with more severe late effects and intensive therapy. Our findings support the idea of response bias.

The occupational rehabilitation course improved physical fitness and decreased overweight in long-term survivors of ALL, but impaired their HRQoL. The survivors with the most severe late effects ended up on disability retirement despite rehabilitation. Our study emphasizes the need for organized late follow-up of cancer survivors, preferably at special follow-up clinics.

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Original publications

This list is based on the following publications, which are referred to in the text by their Roman numerals I-IV:

- I. Harila Marika J, Winqvist Satu, Lanning Marjatta, Bloigu Risto & Harila-Saari Arja H (2009) Progressive Neurocognitive Impairment in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 53: 156–161.
- II. Harila Marika J, Salo Jarmo, Lanning Marjatta, Vilkkumaa Ilpo & Harila-Saari Arja H (2010) High Health-Related Quality of Life Among Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 55: 331–336.
- III. Harila Marika J, Niinivirta Tomi IT, Winqvist Satu & Harila-Saari Arja H (2011) Low depressive symptom and mental distress scores in adult long-term survivors of childhood acute lymphoblastic leukaemia. *J Pediatr Hematol Oncol* 33(3): 194–8.
- IV. Harila Marika, Haapala Eija, Vilkkumaa Ilpo & Harila-Saari Arja Efficacy of occupational rehabilitation intervention in long-term survivors of acute lymphoblastic leukemia. Manuscript

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